Document Type: Protocol, Amendments and SAP

Official Title: A Randomized, Open-Label, Multicenter, Phase II Trial Evaluating the Safety and Activity of Pinatuzumab Vedotin (DCDT2980S) in Combination With Rituximab or Polatuzumab Vedotin (DCDS4501A) in Combination With Rituximab and a Non-Randomized Phase Ib/II Evaluation of Polatuzumab Vedotin in Combination With Obinutuzumab in Patients With Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma

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Protocol Amendment Version 3: 30-Apr-2015

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Protocol Amendment Version 1: 24-Jun-2013

PROTOCOL

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF PINATUZUMAB VEDOTIN (DCDT2980S) IN COMBINATION WITH RITUXIMAB OR POLATUZUMAB VEDOTIN (DCDS4501A) IN COMBINATION WITH RITUXIMAB AND A NON-RANDOMIZED PHASE IB/II EVALUATION OF POLATUZUMAB VEDOTIN IN COMBINATION WITH OBINUTUZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
VERSION NUMBER:	A4
EUDRACT NUMBER:	2011-004377-84
IND NUMBER:	107713
STUDY DRUG:	Pinatuzumab vedotin (DCDT2980S); polatuzumab vedotin (DCDS4501A)
MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	Genentech, Inc.
DATE FINAL:	27 July 2012
DATES AMENDED:	Version A1: 24 June 2013 Version A2: 6 November 2014 Version A3: 30 April 2015 Version A4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	03-Oct-2017 17:09:03

PROTOCOL AMENDMENT, VERSION A4: RATIONALE

Protocol GO27834 has been amended to implement the following changes:

- Language has been updated to include ^{18}F-fluorodeoxyglucose–positron emission tomography (^{18}F-FDG-PET; hereafter referred to as PET)/computed tomography (CT) scans as a response assessment. Lugano Response Criteria is based upon PET/CT as a modality. PET/CT is a correction to comply with the standard Lugano Response Criiteria (Cheson 2014; Sections 2.1, 2.2.2, 2.3.1, 3.3.3., 3.3.4, 4.5.1.8, and 4.10.4, and Appendices C–1 and C–2).
- Section 3.4.4 (Risks Associated with ADCETRIS® [Brentuximab Vedotin]) has been deleted and other sections re-numbered accordingly. Brentuximab is a drug produced by Seattle Genetics. It's safety profile was used as a benchmark for potential safety issues, but is now no longer considered relevant with the body of experience available for pinaturzumab (DCDT2980S) and polatuzumab (DCDS4501A).
- Language has been updated to include second malignancies as an adverse event of special interest in all studies containing obinutuzumab (Section 5.1.3).
- Language has been updated to state second malignancies will be recorded indefinitely (even if the study has been closed) for all subjects enrolled in the obinutuzumab containing cohorts and irrespective of new anti-lymphoma treatments (Sections 5.2.1. and 5.6 and Appendices A–1, A–2, and A–3).
- The Medical Monitor has changed and the contact information has been revised (Section 5.4.1).
- Appendix A–5 has been updated to correct visits to occur at 3-month and 6-month intervals as opposed to the erroneous footnote which notes "two-month" and "four-month" intervals.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION A4:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 2.1: PRIMARY OBJECTIVES

The primary objectives of this study are the following:

- To assess the anti-tumor activity of the combination of DCDS4501A and obinutuzumab in patients with relapsed or refractory follicular NHL and DLBCL based on ^{18}*F-fluorodeoxyglucose–positron emission tomography (^{18}F-FDG-PET; hereafter referred to as PET)/computed tomography (CT)* CR at the end of treatment according to Independent Review Committee (IRC) per Lugano 2014 response criteria

SECTION 2.2.2: Activity Objectives

The secondary activity objectives for obinutuzumab-containing arms of the study are the following:

- CR at end of treatment based on PET*/CT* ~~alone~~, as determined by the investigator
- Objective response (OR; CR or PR) at end of treatment based on PET*/CT,* ~~alone~~ as determined by investigator and IRC
- OR *(CR or PR)* at end of treatment based on CT only, as determined by the investigator and IRC
- Best objective response (BOR, CR or PR) while on study based on PET*/CT* ~~alone~~ or CT only, as determined by the investigator

SECTION 2.3.1: Efficacy Objectives

The exploratory efficacy objectives for this study are to evaluate the long-term outcome of obinutuzumab-treated patients according to Lugano 2014 response criteria, as measured by the following:

- Duration of response based on *PET/CT* ~~PET~~ and/or CT scans*, as determined by the investigator*
- Progression-free survival (PFS) based on PET*/CT* and/or CT scans*, as determined by the investigator*
- Event-free survival (EFS) based on PET*/CT* and/or CT scans*, as determined by the investigator*

SECTION 3.3.3: Activity Outcome Measures

The following activity outcome measures will be assessed for obinutuzumab-containing cohorts (Cohorts E, G, and H) according to Lugano 2014 Response Criteria (Cheson et al. 2014):

The primary activity outcome measure will be assessed by:

- CR at end of treatment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) based on PET/*CT* ~~alone~~, as determined by the IRC

The following secondary efficacy outcome measures will be assessed:

- OR (CR or PR) at end of treatment based on PET/*CT*, ~~alone~~ as determined by the investigator and IRC
- BOR (CR or PR) while on study based on PET/*CT* ~~alone~~ or CT only, as determined by the investigator

SECTION 3.3.4: Exploratory Outcome Measures

The following exploratory efficacy outcome measures will be assessed:

- DOR, defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse, or death from any cause, for the subgroup of patients with a best overall response of CR or PR, based on PET/*CT* and/or CT scans as determined by the investigator assessment. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the DOR will be censored on the date of last disease assessment.
- PFS, defined as the time from date of randomization or first treatment (for G-containing arms) to the first occurrence of progression or relapse, or death from any cause , based on PET/*CT* and/or CT scans as determined by the investigator assessment.
- EFS, defined as the time from date of randomization or first treatment (for G-containing arms) to any treatment failure including disease progression relapse, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first, based on PET/*CT* and/or CT scans as determined by the investigator assessment

~~SECTION 3.4.4: Risks Associated with ADCETRIS® (Brentuximab Vedotin)~~

~~An ADC using the same MMAE drug and linker as that used in DCDT2980S and DCDS4501A, but coupled to an antibody targeting the CD30 antigen (brentuximab vedotin, ADCETRIS®, Seattle Genetics), was recently approved by the FDA for use in the treatment of specific subsets of patients with relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma.~~

~~The most common adverse reactions observed in studies with brentuximab vedotin (occurring in at least 20% of patients) were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting.~~

~~Serious adverse reactions were reported in 31% of patients receiving ADCETRIS®. The most common occurring in >2% of patients included peripheral motor neuropathy, abdominal pain, septic shock, supraventricular arrhythmia, pain in extremity, and urinary tract infection. In addition, John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has been reported.~~

~~Because of the use of the same MMAE drug, it is possible that the adverse events observed with the use of brentuximab vedotin can also be observed with the use of DCDT2980S and DCDS4501A.~~

~~Refer to the current version of the ADCETRIS® Prescribing Information for full and updated details.~~

SECTION 4.5.1.8: Tumor Response Assessments

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, on the basis of physical examinations, CT scans, PET/*CT* scans, and/or MRI scans, and bone marrow examinations, using standard response criteria for NHL (Cheson et al. 2007; Cheson et al. 2014) (see Appendix C-1 and C-2). *Specific response assessment criteria differ between the rituximab-containing arms/cohorts and the obinutuzumab-containing cohorts (see Section 4.5.1.8a. and 4.5.1.8b).*

a. Radiographic Assessments for Patients on Rituximab-Containing Arms/Cohorts

A PET/*CT* scan is required during screening for all patients with DLBCL. An additional PET/*CT* scan in ~~DLBCL~~ patients *with DLBCL* should be obtained at the 6-month tumor assessment to ensure consistency of response assessment methodology at this timepoint for all patients. PET/*CT* scans should additionally be obtained to confirm disappearance of metabolically active disease during study treatment and to confirm a CR upon discontinuation of study treatment.

For patients with FL, PET/*CT* scans are not required but may be obtained on the basis of physician preference and if permitted by local health authorities. Similarly, for *patients with* DLBCL, PET/*CT* scans on patients with FL should be obtained during screening; for patients whose tumors are PET positive during screening, an additional PET/*CT* scan should be obtained at the 6-month tumor assessment. PET/*CT* scans should additionally be obtained to confirm disappearance of metabolically active disease during study treatment and to confirm a CR upon discontinuation of study treatment.

For all patients regardless of disease subtype, combined PET/*CT*-~~CT~~ scans may be used instead of CT alone if performed with contrast and if collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent PET/*CT*-~~CT~~ scans. If a PET/*CT*-~~CT~~ scan is to be used during

screening, then PET/*CT* ~~CT~~ scans should be performed for all subsequent tumor assessments in order to ensure their consistency across different timepoints.

b. Radiographic Assessments for Patients on Obinutuzumab-Containing Cohorts

PET/*CT* scans should minimally extend from skull-base to mid-thigh. Full-body PET scan should be performed when clinically appropriate.

PET/*CT* ~~and CT~~ scans are required for *patients with* follicular NHL and DLBCL ~~patients~~ at screening, after Cycle 4 of study treatment (i.e., between Cycle 4 Day 15 and Cycle 5 Day 1), and at EOT. The EOT response assessment should be performed 6–8 weeks after Cycle 8 Day 1 or last study treatment. CT scans without PET scans will be obtained every 6 months for 2 years, with use of Lugano 2014 Response Criteria for NHL (see Appendix C-2).

d. Schedule of Tumor Response Assessments for Rituximab-Containing Arms/Cohorts

Tumor response assessments will be performed every 3 months (±1 week) from the initiation of study treatment until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). The schedule of tumor assessments is independent of the study treatment dose schedule. For patients enrolled in rituximab-containing arms/cohorts, the schedule of tumor response assessments is detailed in Appendix A-1. As stated above, for all patients with DLBCL enrolled in a rituximab-containing arm/cohort, PET/*CT* scans are required during the screening period and at the 6-month tumor assessment timepoint.

e. Schedule of Tumor Response Assessments for Obinutuzumab-Containing Cohorts

All patients with follicular NHL and DLBCL enrolled in obinutuzumab-containing cohorts are required to have a combined PET/*CT* ~~and CT~~ scan at screening, after Cycle 4 of treatment, and at EOT. The schedule for tumor response assessments for patients enrolled in obinutuzumab-containing cohorts is detailed in Appendix A-3.

SECTION 4.10.4: Activity Analyses

For patients *in the rituximab-containing arms/cohorts* with DLBCL, primary assessment of tumor response will be based on diagnostic imaging scans~~—~~for example, CT and/or MRI scans and PET/*CT* scans. For patients with FL enrolled in the rituximab-containing arms/cohorts, primary assessment of response will be based on CT scans only; the assessment of response in patients with FL based on PET/*CT* scans will be performed for exploratory purposes only.

SECTION 5.1.3: ~~Non Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)~~*Protocol-Defined Adverse Events of Special Interest/Non-Serious Expedited Adverse Events*

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions), irrespective of regulatory seriousness criteria. Adverse events of special interest for this study include the following:

- *Secondary malignancies*

SECTION 5.2.1: Adverse Event Reporting Period

After initiation of study drug (the Genentech product[s] or other IMP), all new AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment *with the exception of second malignancies* (see Section 5.6). *Second malignancies will be recorded indefinitely (even if the study has ended) and irrespective of new anti-lymphoma treatment (NALT).*

SECTION 5.4.1: Reporting Requirements for Fatal/Life Threatening SAEs Related to Investigational Product

Medical Monitor Contact Information for sites in North America:

Medical Monitor: [redacted], *M.D.*

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

SECTION 5.6: POST STUDY ADVERSE EVENTS

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt to be related to prior study treatment. *Second malignancies will be recorded indefinitely (even if the study has been closed) and irrespective of NALT.* The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to Genentech Drug Safety on the study eCRF. If the study eCRF is no longer available, the investigator should report the event directly to Genentech Drug Safety either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided below.

APPENDIX A–1: Study Flowchart: Initial Study Treatment (Arms A–B, Cohorts C–D)

The study flowchart for initial study treatment has been revised to reflect the changes to the protocol.

APPENDIX A–2: Study Flowchart: Crossover Treatment (Patients Randomized to Arms A or B Only)

The study flowchart for crossover treatment has been revised to reflect the changes to the protocol.

APPENDIX A–3: Study Flowchart for Obinutuzumab-Containing Cohorts (E, G–H): Initial Study Treatment

The study flowchart for for obinutuzumab-containing cohorts has been revised to reflect the changes to the protocol.

APPENDIX A–5: Post-Treatment Follow-Up for Obinutuzumab-Containing Regimens (Cohorts E, G-H)

The post-treatment follow-up for obinutuzumab-containing regimens has been revised to reflect the changes to the protocol and to correct visit intervals.

APPENDIX C–1: Modified Response and Progression Criteria for NHL

Appendix C–1 has been revised to reflect the changes to the protocol.

APPENDIX C–2: Revised Criteria for Response Assessment: The Lugano Classification (Cohorts E, G–H)

Appendix C–2 has been revised to reflect the changes to the protocol.

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TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF PINATUZUMAB VEDOTIN (DCDT2980S) IN COMBINATION WITH RITUXIMAB OR POLATUZUMAB VEDOTIN (DCDS4501A) IN COMBINATION WITH RITUXIMAB AND A NON-RANDOMIZED PHASE IB/II EVALUATION OF POLATUZUMAB VEDOTIN IN COMBINATION WITH OBINUTUZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
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MEDICAL MONITORS:	[redacted], *M.D.*
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return a copy of the form to the CRO Monitor at your site. Please retain the original for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF PINATUZUMAB VEDOTIN (DCDT2980S) IN COMBINATION WITH RITUXIMAB OR POLATUZUMAB VEDOTIN (DCDS4501A) IN COMBINATION WITH RITUXIMAB AND A NON-RANDOMIZED PHASE Ib/II EVALUATION OF POLATUZUMAB VEDOTIN IN COMBINATION WITH OBINUTUZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
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STUDY DRUG:	Pinatuzumab vedotin (DCDT2980S); polatuzumab vedotin (DCDS4501A)
PHASE:	II
INDICATION:	Relapsed or refractory B-cell non-Hodgkin's lymphoma
SPONSOR:	Genentech, Inc.

Objectives

Primary Objectives

The primary objectives of this study are the following:

- To assess the safety and tolerability of the combination of DCDT2980S and rituximab administered to patients with relapsed or refractory follicular non-Hodgkin's lymphoma (NHL) and diffuse large B-cell lymphoma (DLBCL)
- To assess the safety and tolerability of the combination of DCDS4501A and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the safety and tolerability of the combination of DCDS4501A and obinutuzumab when administered to patients with relapsed or refractory follicular NHL or DLBCL
- To assess the anti-tumor activity of the combination of DCDT2980S and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and obinutuzumab in patients with relapsed or refractory follicular NHL and DLBCL based on ^{18}*F-fluorodeoxyglucose–positron emission tomography (*^{18}*F-FDG-PET; hereafter referred to as PET)/computed tomography (CT)* complete response (CR) at the end of treatment according to Independent Review Committee (IRC) per Lugano 2014 response criteria

The secondary safety objectives of this study are the following:

- To assess the incidence of antibody formation to DCDT2980S, DCDS4501A, and obinutuzumab as measured by the formation of anti-therapeutic antibodies (ATAs)
- To compare the safety and tolerability of the combination of DCT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab

Activity Objectives

The secondary activity objective for rituximab-containing arms of the study is the following:

- To compare the anti-tumor activity of the combination of DCT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab

The secondary activity objectives for obinutuzumab-containing arms of the study are the following:

- CR at end of treatment based on PET/CT, as determined by the investigator
- Objective response (OR; CR or partial response [PR]) at end of treatment based on PET/CT as determined by investigator and IRC
- CR at end of treatment based on CT only as determined by the investigator and IRC
- OR $(CR\ or\ PR)$ at end of treatment based on CT only, as determined by the investigator and IRC
- Best objective response (BOR, CR or PR) while on study based on PET/CT or CT only, as determined by the investigator

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives of this study are the following:

- To characterize the pharmacokinetics of DCDT2980S and rituximab in patients with relapsed or refractory NHL when the two drugs are given in combination
- To characterize the pharmacokinetics of DCDS4501A and rituximab or obinutuzumab in patients with relapsed or refractory NHL when the two drugs are given in combination

Patient-Reported Outcome Objectives

The objective of this study related to assessment of patient-reported outcomes (PRO) is the following:

- To assess patient-reported tolerability to study treatment and the impact of study treatment on patient functioning, on the basis of PRO in Rituximab cohorts only

Biomarker Objectives

The objectives of this study related to assessment of biologic markers are the following:

- To make a preliminary assessment of biologic markers that might act as predictors of DCDT2980S + rituximab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL
- To make a preliminary assessment of biologic markers that might act as predictors of DCDS4501A + rituximab or obinutuzumab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL

Study Design

Description of Study

This is a Phase Ib/II, multicenter, open-label study. Up to approximately 246 patients with relapsed or refractory follicular lymphoma (FL) and DLBCL will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data. Arms A and B and Cohort C are no longer enrolling patients.

For Obinutuzumab Cohorts:

Only investigational sites in the United States will enroll patients into Cohort E. Investigational sites in the United States and worldwide will participate in Cohorts G and H.

The study will be composed of a randomized portion and a non-randomized portion, as described in the protocol.

Rituximab-Containing Regimens with DCDT2980S or DCDS4501A

Randomized Portion of the Study (Arms A and B) – Closed to Enrollment

Following determination of eligibility, patients within each disease group will be randomized in a 1:1 ratio to receive one of two treatments:

- Arm A: Rituximab (375 mg/m^2) followed by DCDT2980S (2.4 mg/kg) every 21 days;
- Arm B: Rituximab (375 mg/m^2) followed by DCDS4501A (2.4 mg/kg) every 21 days

The first day of treatment constitutes Day 1 of each cycle. A typical cycle is 21 days in duration.

A dynamic hierarchical randomization scheme will be employed with respect to the following stratification factors:

- For patients with FL (see the protocol for definitions)

  Rituximab refractory disease (no response or disease relapse $<$ 6 months from last rituximab treatment) versus rituximab relapsed disease (disease relapse after response $\geq$ 6 months from last rituximab treatment)

- For patients with DLBCL (see the protocol for definitions)

  Second-line versus third-line (or beyond) therapy

  For second-line patients, disease relapse or no objective response (CR, unconfirmed CR [CRu], or PR) <12 months from the start of initial therapy versus disease relapse, after initial objective response (CR, Cru, or PR), $\geq$ 12 months from start of initial therapy

  For third-line patients, failure to achieve a CR or progression < 6 months from start of most recent therapy versus CR or progression ≥ 6 months from start of most recent therapy

No formal testing comparing the two treatment arms in the randomized portion of the study is planned.

Non-Randomized Portion of the Study with Rituximab (Cohorts C and D)—Closed to Enrollment

Only select investigator sites that have agreed to participate in the non-randomized portion of the study will enroll patients into these cohorts.

Patients with relapsed or refractory follicular NHL will be enrolled in Cohorts C and D to receive rituximab (375 mg/m^2) combined with DCDT2980S or DCDS4501A at a dose of 1.8 mg/kg. The first day of treatment constitutes Day 1 of each cycle. A typical cycle will be 21 days in duration.

The opening of either or both cohorts will be at the Sponsor's discretion and only after the enrollment of patients with FL into the randomized portion of the study is completed. Patients will not be randomized to receive one treatment or the other. It is anticipated that Cohort C and D will be opened sequentially.

All Patients on Rituximab-Containing Arms/Cohorts

All patients on rituximab-containing regimens, regardless of assigned arm/cohort, will receive DCDT2980S or DCDS4501A and rituximab administered by intravenous (IV) infusion on a 21-day cycle. For the first two cycles, rituximab will be administered by IV infusion on Day 1 and DCDT2980S or DCDS4501A will be administered by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this instance, rituximab will be administered first, followed by DCDT2980S or DCDS4501A. In certain circumstances—for example, infusion-related reactions (IRRs) requiring interruption or slowing of infusion rate—rituximab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDT2980S or DCDS4501A may be administered on Day 2 following completion of the rituximab infusion or on Day 3 of the cycle.

Patients may receive treatments for up to 1 year (17 cycles on an every-21-day schedule) if not discontinued because of significant toxicity, disease progression, or withdrawal from study.

Patients will be evaluated for safety and efficacy according to the Schedules of Assessments outlined in the protocol. Initial response assessments in this study will be performed every 3 months from the initiation of therapy until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). Additional response assessments for patients who proceed to crossover treatment will be performed as described in the protocol; response assessments for patients who discontinue study treatment (both initially assigned treatment and crossover treatment) for reasons other than disease progression will be performed as described in the protocol.

Responses to study treatment will be based on investigator assessments. In addition, tumor assessment data will be transmitted to an Independent Review Facility (IRF) for collection and possible independent review.

Obinutuzumab-Containing Regimens with DCDS4501A (Cohorts E, G, and H)—Closed to Enrollment

DCDS4501A at 1.8 mg/kg will be given in combination with obinutuzumab to patients with relapsed or refractory follicular NHL and DLBCL in two stages: (1) safety run-in and (2) expansion.

Study treatment will be given in 21-day cycles for both follicular NHL and DLBCL. Patients will be treated for up to a total of 8 cycles. For the first cycle, obinutuzumab will be administered by IV infusion on Days 1, 8, and 15. DCDS4501A will be given on Day 2 for Cycle 1. In the absence of any infusion-related adverse events, obinutuzumab and DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the second cycle. If obinutuzumab and DCDS4501A are administered on the same day, the study drugs will be given sequentially. Obinutuzumab will be administered first, followed by DCDS4501A. In certain circumstances—for example, IRRs requiring interruption or slowing of infusion rate—obinutuzumab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDS4501A may be administered on Day 2 following completion of the obinutuzumab infusion.

Obinutuzumab-Containing Regimen in Phase Ib: Safety Run-In (Cohort E)

This portion of the study will consist of a safety run-in that will evaluate the safety of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in 6 patients (Cohort E). The safety run-in is described in detail in the protocol.

Obinutuzumab-Containing Regimens in Phase II: Expansion Stage (Cohorts G and H)

After the safety run-in has demonstrated that DCDS4501A at 1.8 mg/kg in combination with obinutuzumab is safe to administer, patients will be enrolled into two expansion cohorts based on histology of follicular NHL or DLBCL (Cohorts G and H respectively). Forty patients will be enrolled into each expansion cohort. An additional cohort(s) may be added in the future.

Follicular NHL Patients for Rituximab-Containing Arms/Cohorts

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed to regimens containing rituximab, defined as documented history of response (CR, CRu, or PR) of $\geq$6 months in duration from completion of all prior rituximab-containing regimens. A rituximab-containing regimen is defined as rituximab as a single agent during induction and/or maintenance or in combination with other agents during induction and/or maintenance.

- Refractory to any prior regimen containing rituximab, defined as no response to or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:

  Patients with progressive disease while receiving rituximab monotherapy, rituximab combined with chemotherapy, or rituximab maintenance therapy; patients must have received at least one full dose (375 mg/m^2) of rituximab.

  Patients with no objective response (PR or CR) to a rituximab-containing regimen consisting of at least 4 weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

  Patients with disease relapse, after having achieved an objective response, within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Enrollment of patients with refractory disease as defined above may be limited to no greater than 60% of the total follicular NHL cohort, in order to avoid overrepresentation of the refractory disease population.

Follicular NHL Patients for Obinutuzumab-Containing Cohorts

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed to prior regimen(s) after having a documented history of response (CR, CRu, or PR) of ≥ 6 months in duration from completion of regimen(s)
- Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy

DLBCL Patients for Rituximab-Containing Arms/Cohorts

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/stem cell transplant (SCT) will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (stable disease [SD]) < 12 months from start of initial therapy (second-line refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response ≥ 12 months from start of initial therapy (second-line relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) < 6 months from start of prior therapy (third-line + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response ≥ 6 months from start of prior therapy (third-line + relapsed)

Enrollment into any of the above four categories may be limited to no greater than 40% of the DLBCL cohort—and to no more than 60% of the two refractory categories combined—to avoid overrepresentation of any specific subpopulation, refractory patients in particular.

DLBCL Patients for Obinutuzumab-Containing Cohorts

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/SCT as determined by the investigator will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) < 12 months from start of initial therapy (second-line refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response ≥ 12 months from start of initial therapy (second-line relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) < 6 months from start of prior therapy (third-line + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response ≥ 6 months from start of prior therapy (third-line + relapsed)

Crossover Treatment (Randomized Patients in Arms A and B Only)

Patients randomized to Arm A or Arm B who develop progressive disease may be eligible to receive crossover treatment consisting of rituximab and the other antibody-drug conjugate (ADC) or the other ADC alone—for example, Arm B treatment for patients who have disease progression while receiving Arm A treatment, and vice versa—provided the following conditions are met:

- Patients must not have experienced a toxicity requiring the discontinuation of DCDT2980S/DCDS4501A treatment OR experienced toxicity during the last dose of study treatment that would preclude treatment with the crossover regimen.

  Patients who had modifications to dosing and/or schedule on the initial study treatment will be permitted to receive crossover treatment in the absence of toxicities on the modified dose and/or schedule. The dose and schedule of crossover treatment will be determined by the investigator and the Medical Monitor.

  Patients who had rituximab discontinued and continued on single-agent DCDT2980S/DCDS4501A treatment may receive crossover treatment of single-agent DCDS4501A/ DCDT2980S.
- Patients must have radiographically documented disease progression.
- Patients must meet all inclusion and exclusion criteria described in the Inclusion Criteria and Exclusion Criteria sections below, except for those related to prior rituximab treatment.
- Acceptable toxicity: All study drug–related adverse events from the initial study treatment must have decreased to Grade 1 or baseline grade on or before the first day of treatment on the crossover regimen. Exceptions may be allowed after a careful assessment and discussion of the benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.
- Administration of crossover treatment must be in the best interests of the patient as determined after a careful assessment and discussion of benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.
- A tumor biopsy (described in the protocol) will be required for patients with safely accessible site of disease, defined as requiring only local anesthesia and, in general, excluding the brain, lungs or any internal organs that may subject patients to significant risk.

  Patients for whom a safely accessible site of disease is not present may still receive crossover treatment without undergoing a biopsy. Eligibility to receive crossover treatment should be discussed with and approved by the Medical Monitor.

  A tumor biopsy of a safely accessible site of disease is optional for patients who are not eligible for study cross over.

Patients who are determined to be eligible for study cross over will be treated as follows:

- Assessments obtained at the initial study treatment discontinuation visit (described in the protocol) may be used as screening assessments for crossover treatment. The following re-screening assessments must be repeated/obtained within 1 week prior to starting treatment on the crossover regimen, in order to re-establish baseline pretreatment clinical and disease status: targeted physical exam, Eastern Cooperative Oncology Group (ECOG) status, and hematology and serum chemistry laboratory tests.

  Re-screening tests for hepatitis B and C do not need to be performed unless there is clinical suspicion of hepatitis B and/or C positivity.

  A radiographic tumor assessment must also be performed, unless already done to document disease progression, within 6 weeks prior to starting crossover treatment.
- Crossover treatment will begin no later than 42 days after the last dose of the prior study treatment.

Patients will be treated with the crossover treatment until a second disease progression event relative to the tumor assessment, documenting progressive disease on the initial study treatment, clinical deterioration, and/or intolerance to the crossover treatment for up to a maximum of 1 year (17 cycles on an every-21-day schedule). Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in the protocol.

Response assessments for patients who discontinue study treatment for reasons other than disease progression will be performed as described in the protocol.

Clinical data and exploratory data derived from tumor biopsies obtained prior to crossover treatment will be monitored on an ongoing basis. Genentech has the right to restrict or suspend enrollment into crossover treatment at any time. Reasons for this may include, but are not limited to, the following:

- The incidence or severity of adverse events during crossover treatment indicates a potential safety hazard to patients.
- Patient enrollment into crossover treatment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Patients who are enrolled into the non-randomized portion of the study (Cohorts C, D, E, G, and H) will not have the option to receive crossover treatment upon disease progression.

Number of Patients

Up to approximately 246 patients with relapsed or refractory FL and DLBCL will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form(s)
- Age ≥ 18 years
- ECOG Performance Status of 0, 1, or 2
- Life expectancy of at least 12 weeks
- History of histologically documented relapsed or refractory Grades 1–3a FL or relapsed or refractory DLBCL
- Availability of an archival or freshly biopsied tumor tissue sample must be confirmed for study enrollment.
- Have a clinical indication for treatment as determined by the investigator
- Must have at least one bidimensionally measurable lesion (> 1.5 cm in its largest dimension by computed tomography [CT] scan or magnetic resonance imaging [MRI])
- Laboratory values (including patients with hepatic or renal involvement), as follows:

  AST and ALT $\leq 2.5 \times$ ULN

  Total bilirubin $\leq 1.5 \times$ ULN

  Platelet count $\geq 75{,}000/mm^3$ (unless thrombocytopenia clearly due to marrow involvement of NHL and/or disease-related immune thrombocytopenia)

  Absolute neutrophil count $\geq 1000/mm^3$ (without growth factor support, unless neutropenia clearly due to marrow involvement of NHL)

  Total hemoglobin ≥ 9 g/dL (without transfusion support > 14 days prior to screening, unless anemia clearly due to marrow involvement of NHL)

  Serum creatinine ≤ 2.0 mg/dL or measured creatinine CL ≥ 50 mL/min
- For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one highly effective form of nonhormonal contraception or two effective forms of nonhormonal contraception, **including at least one method with a failure rate of <1% per year**, through the course of study treatment and for $\geq$ 12 months after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab (whichever is later) in women and at least 5 months after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab (whichever is later) in men

A woman is considered not to be of childbearing potential if she is postmenopausal, defined by amenorrhea of ≥12 months duration and age ≥45 years, or has undergone hysterectomy and/or bilateral oophorectomy.

The following are considered highly effective forms of contraception: 1) true abstinence; 2) male sterilization (with post-procedure documentation of absence of sperm in the ejaculate). For female patients, the sterilized male partner should be the sole partner.

The following are considered effective forms of contraception: 1) intrauterine device (IUD; copper IUD or hormonal IUDs only) or intrauterine system; 2) condom with spermicidal foam/gel/film/cream/suppository; 3) occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.

Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S or, DCDS4501A or, rituximab, or obinutuzumab (whichever is later).

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Prior use of any MAb, radioimmunoconjugate or ADC within 4 weeks before Cycle 1, Day 1
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational anti-cancer agent within 2 weeks prior to Cycle 1, Day 1

  Adverse events except for sensory neuropathy from any previous treatments must be resolved or stabilized to Grade ≤2 prior to Cycle 1, Day 1.
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1, Day 1
- Prior allogeneic stem cell transplant
- Eligibility for autologous SCT (patients with relapsed or refractory DLBCL)
- History of transformation of indolent disease to DLBCL
- History of severe allergic or anaphylactic reactions to MAb therapy (or recombinant antibody-related fusion proteins)
- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma (e.g., of the cervix or breast) are allowed. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥2 years prior to Cycle 1, Day 1.
- Current or past history of CNS lymphoma
- Current Grade >1 peripheral neuropathy
- Evidence of significant, uncontrolled, concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Recent major surgery within 6 weeks prior to Cycle 1, Day 1, other than for diagnosis

- Presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total anti-HBc) or hepatitis C (HCV antibody)

  Patients who are positive for anti-HBc are eligible only if polymerase chain reaction (PCR) is negative for HBV DNA and it is believed by both the investigator and Medical Monitor that it is in the patient's best interest to participate.

  Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.
- Vaccination with a live vaccine within 28 days prior to treatment
- Known history of HIV seropositive status
- Women who are pregnant or lactating
- Ongoing corticosteroid use >30 mg/day prednisone or equivalent

  Patients receiving corticosteroid treatment ≤ 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy

Length of Study

The length of study will be the time from screening of the first enrolled patient through 2 years after the Treatment Completion Visit for the last enrolled patient on an obinutuzumab-containing regimen. The length of the study for the obinutuzumab-containing cohorts is expected to be approximately 48 months.

End of Study

The end of study is defined as the timepoint at which patients enrolled in the obinutuzumab-containing regimens in the study have had at least 2 years of follow-up from the time of the Treatment Completion Visit or have discontinued from the study.

Outcome Measures

Safety Outcome Measures

The safety and tolerability of the combination of DCDT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab will be assessed using the following safety outcome measures:

- Incidence, nature, and severity of adverse events
- Incidence of anti-DCDT2980S, anti-DCDS4501A, or anti-obinutuzumab antibodies
- Changes in vital signs
- Changes in laboratory values

The determination of the DCDS4501A RP2D in combination with obinutuzumab will be assessed using the following primary safety outcome measures for the Phase Ib portion of the study:

- Incidence and nature of DLTs
- Incidence, nature, and severity of adverse events and serious adverse events
- Changes in vital signs, physical findings, ECGs, and clinical laboratory values during and following study treatment administration

Pharmacokinetic/Pharmacodynamic Outcome Measures

The following PK parameters will be derived from the serum concentration–time profiles of total antibody (the sum of conjugated and unconjugated antibody), including rituximab or obinutuzumab, and plasma concentration-time profiles of antibody-conjugated monomethyl auristatin E (acMMAE) and free MMAE following administration of DCDT2980S or DCDS4501A, when appropriate, as data allow:

- Total exposure (area under the concentration-time curve [AUC])
- Maximum plasma and serum concentration (C_{max})
- Clearance (CL)

- Terminal half-life ($t_{1/2}$)
- Steady-state volume of distribution (V_{ss})

Compartmental, non-compartmental, and/or population methods may be used. Other parameters, such as accumulation ratio and trough plasma and serum concentration (C_{min}), may also be calculated.

The following PD outcome measures will be assessed when appropriate, as data allow:

- Peripheral blood B-cell depletion and recovery. For each visit at which $CD19^+$ B-cell measurements are taken, B-cell data will be listed for each patient by dose level as follows:

  Absolute blood cell counts

  Percent change relative to the baseline blood counts

  $CD19^+$ B-cell recovery, defined as the timepoint when the values return to baseline levels or $\geq$50% of baseline levels

Activity Outcome Measures

The following activity outcome measures will be assessed for rituximab-containing arms/cohorts (Arms A and B, Cohort C):

- Objective response, defined as a PR or CR
- Duration of objective response, defined as the duration of time from the first occurrence of a documented objective response to time of relapse or death from any cause
- Progression-free survival (PFS), defined as the duration from initial randomization to the first occurrence of progression or death within 30 days of the last administration of study drug, whichever occurs first
- Overall survival (OS), defined as the duration from the date of randomization/enrollment to the date of death from any cause

Objective response and disease progression will be determined using standard criteria for NHL.

The following activity outcome measures will be assessed for obinutuzumab-containing cohorts (Cohorts E, G, and H) according to Lugano 2014 Response Criteria (Cheson et al. 2014):

The primary activity outcome measure will be assessed by:

- CR at end of treatment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) based on PET/*CT*, as determined by the IRC

The following secondary efficacy outcome measures will be assessed:

- OR (CR or PR) at end of treatment based on PET/*CT* as determined by the investigator and IRC
- CR at end of treatment based on CT only, as determined by the investigator and IRC
- OR (CR or PR) at end of treatment based on CT only as determined by the investigator and IRC
- BOR (CR or PR) while on study based on PET/*CT* or CT only, as determined by the investigator

Exploratory Outcome Measures

The exploratory outcome measures will include, but will not be limited to, the following:

- Confirmation and quantitation of CD22, CD79b, and CD20 expression levels in either archival or freshly obtained (when available) tumor specimens (tumor biopsies, bone marrow biopsies, peripheral blood) by immunohistochemistry/flow cytometry/quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)
- Additional assessments related to the understanding of the mechanism of action of DCDT2980S, DCDS4501A, rituximab, and obinutuzumab, mechanisms of resistance to DCDT2980S, DCDS4501A, rituximab, and obinutuzumab, and/or NHL pathogenesis may be included.

- Treatment and disease symptom assessments using the M.D. Anderson Symptom Inventory (MDASI) in rituximab-containing cohorts only

The following exploratory efficacy outcome measures will be assessed:

- DOR, defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse, or death from any cause, for the subgroup of patients with a best overall response of CR or PR, based on PET/CT and/or CT scans as determined by the investigator assessment. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the DOR will be censored on the date of last disease assessment.
- PFS, defined as the time from date of randomization or first treatment (for G-containing arms) to the first occurrence of progression or relapse, or death from any cause, based on PET/CT and/or CT scans as determined by the investigator assessment.
- EFS, defined as the time from date of randomization or first treatment (for G-containing arms) to any treatment failure including disease progression relapse, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first, based on PET/CT and/or CT scans as determined by the investigator assessment
- OS, defined as the time from the date of first treatment to the date of death from any cause

Investigational Medicinal Products

Test Product

Pinatuzumab Vedotin (DCDT2980S) and Polatuzumab Vedotin (DCDS4501A)

Patients will receive DCDT2980S or DCDS4501A at 1.8 mg/kg or 2.4 mg/kg by IV infusion on Day 1 or Day 2 for each cycle. The total dose of DCDT2980S or DCDS4501A for each patient will be determined by the dose cohort to which the patient is assigned and depend on the patient's weight within 96 hours prior to Day 1 of each cycle.

Rituximab

All patients in rituximab-containing arms/cohorts will receive DCDT2980S or DCDS4501A and rituximab administered by IV infusion on a 21-day cycle. For the first two cycles, patients will receive rituximab 375 mg/m^2 by IV infusion on Day 1 and DCDT2980S or DCDS4501A by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab 375 mg/m^2 and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this case, rituximab will be administered first, followed by DCDT2980S or DCDS4501A.

Obinutuzumab

Patients in obinutuzumab-containing cohorts will receive DCDS4501A and obinutuzumab administered by IV infusion on a 21-day cycle. For the first cycle, patients will receive obinutuzumab 1000 mg by IV infusion on Days 1, 8, and 15. DCDS4501A will be given on Day 2 for Cycle 1. In the absence of any infusion-related adverse events, obinutuzumab and DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the second cycle.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

The final analysis will be based on patient data collected until all patients discontinue from the study or the study is terminated by the Sponsor, whichever occurs first. The analyses will be based on the safety evaluable population, defined as patients who received at least one dose of study treatment. All summaries will be presented according to the disease-specific cohort, treatment group, and assigned dose level.

Analysis of the Conduct of the Study

Enrollment, major protocol violations, and reasons for discontinuations from the study will be summarized.

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, duration of malignancy, and baseline ECOG Performance Status, will be summarized using means,

standard deviations, medians, and ranges for continuous variables and proportions for categorical variables. All summaries will be presented overall and by treatment group, assigned dose level, and disease-specific cohort.

Study drug administration data will be listed by the disease-specific cohorts described in the protocol. Any dose modifications will be flagged. Means and standard deviations will be used to summarize the total doses of DCDT2980S, DCDS4501A, rituximab, and obinutuzumab received. All summaries will be presented by treatment group, assigned dose level, and disease-specific cohort.

Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, and changes in vital signs. All patients who receive any amount of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab will be included in the safety analysis and will be assigned to the treatment group on the basis of the study treatment received. Patients who have dose level changes from the initial assigned dose level will be summarized by the initial assigned dose level of DCDT2980S or DCDS4501A.

All adverse event data will be listed by study site, patient number, treatment group, disease-specific cohort, and cycle. All adverse events occurring on or after treatment on Day 1 of Cycle 1 will be summarized by mapped terms, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade. In addition, all serious adverse events, including deaths will be listed separately and summarized.

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to DCDT2980S and DCDS4501A will be summarized.

Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum concentrations of total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) and rituximab or obinutuzumab and plasma concentrations of acMMAE and free MMAE versus time data will be tabulated and plotted by NHL disease subtype (relapsed or refractory follicular NHL or DLBCL). The pharmacokinetics of the above analytes will be summarized by estimating the appropriate PK parameters (e.g., AUC, C_{max}, CL, V_{ss}, and $t_{1/2}$). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and range). Non-compartmental, compartmental, and/or population methods will be used, as data allow.

Exposure-response (safety and efficacy) analysis may be conducted with use of PK data and available drug effect (e.g., imaging, measures of tumor burden) and toxicity (e.g., clinical pathology) data, at the sponsor's discretion.

In addition, population PK methods may be employed to manage sparse data and to investigate the effects of certain covariates on the pharmacokinetics of DCDT2980S and DCDS4501A, as data allow, and at the sponsor's discretion.

Activity Analyses

Best overall response, duration of response, and PFS will be listed for all patients.

Overall response rate (ORR) from the initial study treatment will be calculated on the basis of data from patients who received study treatment. Objective response is defined as CR or PR as determined by the investigator, on the basis of physical examinations, radiographic scans, and bone marrow examinations, using modified response criteria for NHL and confirmed by repeat assessments $\geq$4 weeks after initial documentation. Any patient with insufficient data to determine response will be classified as a non-responder.

For patients *in the rituximab-containing arms/cohorts* with DLBCL, primary assessment of tumor response will be based on diagnostic imaging scans—for example, CT and/or MRI scans and PET/*CT* scans. For patients with FL enrolled in the rituximab-containing arms/cohorts, primary assessment of response will be based on CT scans only; the assessment of response in patients with FL based on PET/*CT* scans will be performed for exploratory purposes only.

For patients on obinutuzumab-containing cohorts, primary response assessment for both DLBCL and FL will be based on PET/CT scans using the updated 2014 Lugano Response Criteria. Patients in Cohorts E, G, and H will be evaluated with a PET/CT scan at screening, between Cycle 4 Day 15 and Cycle 5 Day 1, and at the end of treatment (6-8 weeks after completing treatment). The efficacy analysis for these cohorts will, therefore, be different from

the analysis for Arms A–B and Cohorts C–D. Subsequent imaging can be CT only. Responses to study treatment will also be based on investigator assessments.

Among patients with an objective response, duration of response will be defined as the time from the initial documentation of a CR or PR to the time of disease progression or death. If a patient does not experience death or disease progression before the end of the study, duration of response will be censored at the day of the last tumor assessment.

For the randomized portion of the study (Arms A and B), PFS is defined as the time from the date of randomization to the date of disease progression or death from any cause, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the date of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. For the non-randomized portion of the study (Cohorts C through H), PFS is defined as the time from the date of study enrollment to the date of disease progression or death from any cause, whichever occurs first.

For the randomized portion of the study (Arms A and B), OS is defined as the time from the date of randomization to the date of death from any cause. For the non-randomized portion of the study (Cohorts C through H), OS is defined as the time from the date of study enrollment to date of death from any cause.

Exploratory Analyses

Assay results of possible predictive markers will be listed by treatment group and response status.

Frequencies and percentages of missing data for the PRO endpoints will be reported. Dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) will be summarized.

Summary statistics of the MDASI items, scales, and their changes from baseline will be calculated at each assessment timepoint. The mean, standard error, and median of the absolute scores and the mean changes from baseline (and 95% CI) within and between study arms will be reported for the MDASI scales and single items, as well as the weekly averages of the worst symptom rating. For change scores in the MDASI from baseline, patients without baseline scores will not be included in the analyses. Line charts depicting the means and mean changes of subscales over time will be also provided.

Repeated measures mixed-effects models will explore MDASI subscale scores with a baseline score and appropriate covariates added, as appropriate.

Handling of Missing Data

For the endpoint of objective response, patients without a post-baseline tumor assessment will be considered non-responders in the all-treated population analysis.

For duration of response and PFS, data from patients who are lost to follow-up will be included in the analysis as censored observations on the last date that the patient is known to be progression free, defined as the date of the last tumor assessment, or, if no tumor assessments were performed, as the date of last study treatment plus 1 day.

Compliance to PRO data collection will be reported with summary statistics, including frequencies of reasons for non-compliance such as patient refusal to complete PRO data collection.

Determination of Sample Size

For the randomized portion of the study (Arms A and B), a target of 120 patients will be enrolled in two separate cohorts of patients (40 in the follicular NHL cohort and 80 in the DLBCL cohort). The randomized portion of this study is non-comparative in nature. No formal hypothesis testing is planned to compare the treatment arms. Moreover, there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms. Genentech has judged the proposed sample size to provide sufficient precision in estimating the anti-tumor activity of DCDT2980S combined with rituximab or DCDS4501A combined with rituximab as measured by objective response. For example, with the assumption of an observed response rate of 40%, a 90% confidence interval for the response rate would be approximately 22%–58% (i.e., 40% ± 18%) for the follicular NHL cohort and approximately 27%–53% (i.e., 40% ± 13%) for the DLBCL cohort. With 40 patients, there is an 87% chance of observing at least one adverse event with a true incidence of 5%.

For the non-randomized portions of the study (Cohorts C and D), approximately 20 patients will be enrolled into each arm, for a total of 40 patients. With 20 patients under an observed response rate of 40%, the exact Clopper-Pearson 90% confidence interval for the response rate would be 22%–61%. With respect to the assessment of safety based upon a sample size of 20 patients, the chance of observing at least one adverse event with a true incidence of 10% is 88%.

For the obinutuzumab safety run-in cohort (Cohort E), 6 patients will be enrolled. For the obinutuzumab expansion cohorts (Cohorts G and H), 40 patients with follicular NHL and 40 patients with DLBCL will be enrolled at the RP2D to further evaluate safety and efficacy of the combination. Table 3 in the protocol provides asymptotic 90% confidence intervals for the true probability of response for a range of observed proportions based upon a sample of 40 patients. A sample size of 40 patients is deemed sufficient to provide adequate precision on the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting rate of 45% assuming observed response rates of approximately 60% or higher (~24 responders observed among 40 patients).

Therefore, up to 252 patients may be enrolled in this study.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ac	antibody-conjugated
ADC	antibody–drug conjugate
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
anti-HBc	hepatitis B core antibody
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from 0 to infinity
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma and serum concentration
C_{min}	trough plasma and serum concentration
CR	complete response
CRu	unconfirmed response
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CVP	cyclophosphamide, vincristine, and prednisone
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC	ethics committee
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
^{18}F-FDG-PET	^{18}F-fluorodeoxyglucose–positron emission tomography

Abbreviation	Definition
FACS	fluorescence-activated cell sorting
FBS	fasting blood sugar
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma
G	GA101 or obinutuzumab
G-CHOP	obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HNSTD	highest non-severely toxic dose
HPW	highly purified water
ICH	International Council for Harmonisation
IgG1	immunoglobulin-G1
IHC	immunohistochemistry
IL	interleukin
IMC	Internal Monitoring Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
iNHL	indolent non-Hodgkin's lymphoma
IP	interferon-inducible protein
IRB	Institutional Review Board
IRC	Independent Review Committee
IRF	Independent Review Facility
IRR	infusion-related reaction
ISH	in situ hybridization
IV	intravenous
IxRS	interactive voice or web-based response system
JC	John Cunningham
Kd	equilibrium dissociation constant
LC-MS/MS	liquid chromatography–tandem mass spectrometry
LMWH	low-molecular weight heparin
MCL	mantle cell lymphoma
MC-VC-PABC	maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl

Abbreviation	Definition
MDASI	M.D. Anderson Symptom Inventory
MMAE	monomethyl auristatin E
MAb	monoclonal antibody
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NALT	*new anti-lymphoma treatment*
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NK	natural killer
NOAC	new oral anticoagulant
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PE	polyethylene
PET	positron emission tomography
PD	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PP	polypropylene
PR	partial response
PRO	patient-reported outcomes
PVC	polyvinyl chloride
PUR	polyurethane
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
Q3W	every 3 weeks
R	rituximab
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RP2D	recommended Phase II dose
SAE	serious adverse event
SC	subcutaneous
SCID	severe combined immunodeficiency
SCT	stem cell transplant

Abbreviation	Definition
SD	stable disease
SDV	source data verification
SmPC	Summary of Product Characteristics
STD10	severely toxic dose to 10%
SWFI	Sterile Water for Injection
$t_{1/2}$	terminal half-life
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
ULN	upper limit of normal
Vss	steady-state volume of distribution

1. BACKGROUND

1.1 BACKGROUND ON DISEASE

B-cell lymphoproliferative disorders are a heterogeneous group of malignancies, ranging from slow-growing indolent and incurable diseases with a median survival of 8–10 years (such as follicular non-Hodgkin's lymphoma [NHL]) to more aggressive intermediate- to high-grade lymphomas (such as diffuse large-cell lymphoma), which can have a median survival of 6 months if left untreated or long-term remission in more than 50% of patients with appropriate treatment. Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL accounting for approximately 30%–40% of all new patients, whereas follicular lymphoma (FL) accounts for approximately 20%–25% of new lymphomas.

Despite advances in the clinical outcomes of patients with NHL using treatments such as the CD20-specific monoclonal antibody (MAb) rituximab (Rituxan®, MabThera®) in combination with chemotherapy, indolent B-cell malignancies remain incurable, as do approximately half of aggressive NHL patients. Thus, there is still a need for treatments that can be combined with chemoimmunotherapy and can significantly extend disease-free and overall survival (OS) in these patients, with at least acceptable, if not superior, safety profiles.

1.2 BACKGROUND ON THE MOLECULES

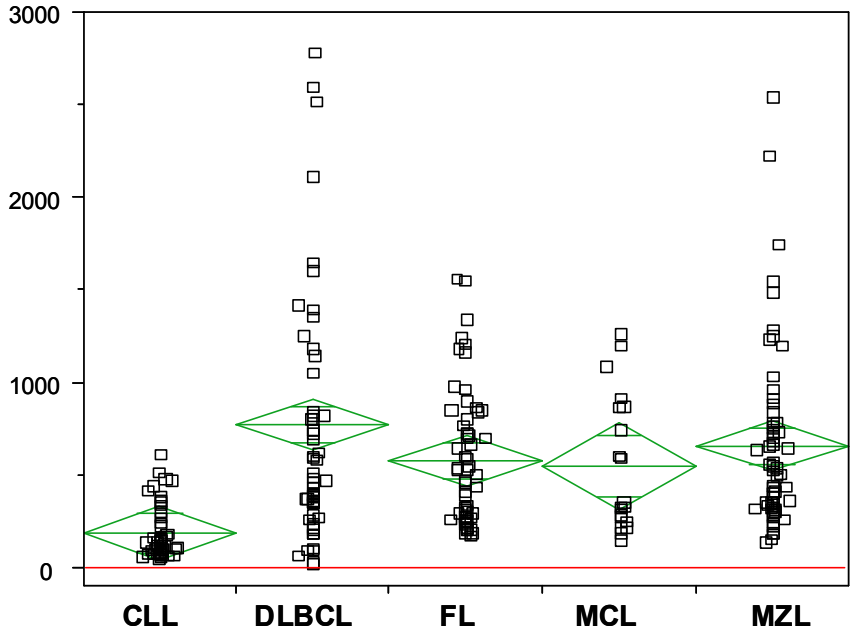
1.2.1 DCDT2980S

1.2.1.1 Background and Preclinical Data

CD22 is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of the B cell–derived malignancies, including nearly all NHL and chronic lymphocytic leukemia (CLL) samples tested (see Figure 1). Antibodies bound to CD22 are rapidly internalized, making CD22 ideally suited for targeted delivery of cytotoxic agents (Shan and Press 1995).

DCDT2980S is an antibody–drug conjugate (ADC) that consists of a potent anti-mitotic agent, monomethyl auristatin E (MMAE) conjugated to a humanized immunoglobulin-G1 (IgG1) anti-CD22 MAb, MCDT2219A, via a protease-labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl (MC-VC-PABC). MMAE has a mode of action similar to vincristine, which is a component of standard chemotherapy used in lymphoma therapy. This therapeutic approach takes advantage of the specific targeting capability of the antibody and the cytotoxic activity of MMAE. Following internalization, the MMAE is deconjugated from DCDT2980S by lysosomal enzymes, binds to tubulin, and disrupts the microtubule network, resulting in inhibition of cell division and cell growth and induction of apoptosis (Doronina et al. 2003).

Figure 1 CD22 Expression Levels on B-Cell Tumor Cells



CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MFI = mean fluorescence intensity; MZL = marginal zone lymphoma.

CD22 expression levels (MFI) on B-cell tumor cells were assessed by flow cytometry in patients diagnosed with the following B-cell lymphomas: CLL (n = 49), DLBCL (n = 59), FL (n = 58), MCL (n = 20), and MZL (n = 60).

Comprehensive pharmacologic, pharmacokinetic (PK), pharmacodynamic (PD), and toxicology evaluations were conducted to support the use of DCDT2980S in clinical trials. DCDT2980S binds human CD22 with a high affinity (equilibrium dissociation constant [K_d] = 1.7 ± 0.2 nM) and showed similar binding affinity to cynomolgus monkey CD22. No binding activity was observed with mouse and rat peripheral blood mononuclear cells (PBMCs).

The unconjugated antibody MCDT2219A did not appear to induce antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) in vitro. In contrast, DCDT2980S displayed potent and selective inhibition of cell proliferation in vitro (50% of the maximal inhibitory concentration [IC_{50}] = 0.33 nM) by cell viability assays. Efficacy studies conducted in murine xenograft models of human lymphoma (CD22-positive WSU-DLCL2 and BJAB cell lines) showed that a single dose of DCDT2980S resulted in regression of tumor growth at doses ranging from 1 to 4 mg/kg. PD studies with DCDT2980S showed that a single dose of 1–6 mg/kg resulted in partial depletion of peripheral blood B cells in cynomolgus monkeys with a corresponding depletion in germinal center B cells in lymphoid tissue.

The PK profiles of DCDT2980S were observed to be linear in rodents and moderately non-linear in cynomolgus monkeys over the tested dose range. The non-linear clearance (CL) observed in cynomolgus monkeys with DCDT2980S is likely due to the contribution of B cell-mediated CL to the total CL. The free MMAE concentrations in cynomolgus monkeys following DCDT2980S administration were generally 10,000 times lower than the concentration of DCDT2980S.

Cynomolgus monkeys were selected as the most relevant nonclinical species for the toxicology and PK/PD studies of DCDT2980S, given the comparable sequence homology of human and cynomolgus monkey CD22, similar binding affinity of DCDT2980S to human and cynomolgus monkey CD22, and comparable tissue cross-reactivity in both human and cynomolgus monkey tissues. DCDT2980S was well tolerated at doses of up to 3 mg/kg (highest non-severely toxic dose [HNSTD]) in monkeys and up to or greater than 10 mg/kg in rats (severely toxic dose to 10% [STD_{10}] of rats $\geq$ 10 mg/kg). Reversible bone marrow toxicity and associated hematopoietic changes were observed in both rats and monkeys treated with DCDT2980S or MMAE, suggesting that the toxicity of DCDT2980S is related to MMAE. Additional effects on liver and lung in rats were minimal in severity and reversible and did not occur in cynomolgus monkeys, which may be due to differences in species sensitivity, exposure, and/or pharmacokinetics.

Complete details of preclinical studies of DCDT2980S can be found in the DCDT2980S Investigator's Brochure.

1.2.1.2 DCDT2980S Clinical Data

a. Patient Enrollment

Both DCDT2980S monotherapy and combination therapy with rituximab have been studied in a Phase I study (Study DCT4862g) of patients with relapsed or refractory B-cell malignancies expected to express CD22, including indolent NHL, DLBCL, mantle cell lymphoma (MCL), and CLL.

All data presented herein is based on a data entry cutoff of 22 February 2013, with clinical data available from 65 patients with NHL (excluding patients with CLL) enrolled in dose-escalation and expansion cohorts. These include 49 patients who were treated with single-agent DCDT2980S at doses ranging from 0.1 to 3.2 mg/kg administered intravenously every 21 days and 16 patients who were enrolled into two Phase Ib cohorts with DCDT2980S administered at doses of 1.8 mg/kg (5 patients) and 2.4 mg/kg (11 patients) in combination with 375 mg/m^2 rituximab.

Enrollment into CLL dose escalation cohorts was closed on 31 May 2013. Refer to the DCDT2980S Investigator Brochure for details regarding clinical data in CLL patients.

b. Pharmacokinetics

The pharmacokinetics of DCDT2980S have been characterized in the Phase I Study DCT4862g. DCDT2980S was administered to patients with NHL at dose levels ranging from 0.1 to 3.2 mg/kg every 3 weeks (Q3W). Three analytes were quantified: antibody-conjugated MMAE (acMMAE), total antibody, and free MMAE.

Preliminary PK analysis based on available data as of 22 June 2012 is summarized below.

The mean value of CL estimates of acMMAE and total antibody of each dose level for doses of ≥ 1.0 mg/kg ranged from 17.6 to 21.3 mL/day/kg and from 10.5 to 16.2 mL/day/kg, respectively. Similar CL estimates for doses ≥ 1.0 mg/kg suggested dose-proportional increase of acMMAE and total antibody exposure. CL estimates appeared to be slightly higher at doses < 1.0 mg/kg (0.1, 0.25, and 0.5 mg/kg), although data from these dose levels are limited. The CL of acMMAE was faster than that of total antibody at each dose level.

In patients with NHL, the mean value of the steady-state volume of distribution (V_{ss}) of acMMAE and total antibody of each dose level ranged from 69.2 to 130 mL/kg and from 97.4 to 154 mL/kg, respectively, across the dose levels tested, approximating human serum volume. V_{ss} values did not appear to change substantially with dose. The half-life for acMMAE and total antibody ranged from 2.9 to 7.0 days and from 4.4 to 13 days, respectively.

For acMMAE and total antibody, the time to maximum concentration occurred immediately after infusion. For free MMAE, the time to maximum concentration was approximately 2 to 3 days after infusion. Maximum plasma and serum concentration (C_{max}) and area under the concentration-time curve from Time 0 to infinity (AUC_{inf}) of free MMAE appeared to increase with dose across the dose levels tested. A half-life of 3-4 days for free MMAE was observed, which is relatively long and similar to that of its parent conjugate, suggesting formation rate–limited kinetics of free MMAE. No accumulation of free MMAE is expected for the Q3W regimen. The C_{max} values of free MMAE in NHL patients were at least 100-fold lower than acMMAE concentrations at each dose level, suggesting a slow release of free MMAE from acMMAE and potentially fast elimination once it is formed.

Preliminary comparisons of pharmacokinetics between patients with NHL and CLL (for which patients are enrolled into separate dose-escalation cohorts) treated with identical doses of DCDT2980S provide some insight into the factors that affect pharmacokinetics. Both acMMAE and total antibody were cleared faster in CLL patients than in NHL patients. This observation is likely to be related to the high number of circulating B cells generally observed in CLL patients, which may result in significant target-mediated CL of DCDT2980S. The free MMAE exposure in CLL patients was relatively low compared to that of its parent conjugate.

The exposure parameters (C_{max} and AUC_{inf}) of total antibody, acMMAE, and free MMAE were similar between DCDT2980S and DCDT2980S + rituximab at doses of 1.8 and 2.4 mg/kg, based on preliminary data. This observation suggests that when given in combination, rituximab does not impact the pharmacokinetics of DCDT2980S; the effect of DCDT2980S on rituximab pharmacokinetics will be assessed.

All observations will be verified with additional data from the ongoing Phase I study as well as this study.

Refer to the DCDT2980S Investigator Brochure for complete and updated details.

c. Safety

Dose Limiting Toxicity

Study DCT4862g utilizes a standard 3+3 dose-escalation cohort enrollment scheme. Patients enrolled into each dose-escalation cohort in Study DCT4862g have been observed for dose-limiting toxicities (DLT) for a minimum of 21 days after their first dose of DCDT2980S. Any patient who did not complete the DLT observation period for any reason other than a DLT was replaced.

Separate dose-escalation cohorts enrolled patients with B-cell NHL and CLL. For the NHL dose escalation, DLTs of Grade 4 neutropenia occurred in 1 patient out of 3 DLT-evaluable patients in the 3.2 mg/kg single-agent cohort and 1 patient out of 11 DLT-evaluable patients in the 2.4 mg/kg + rituximab cohort. Consequently, DCDT2980S at 2.4 mg/kg was determined to be the recommended Phase II dose (RP2D) as both monotherapy and in combination with rituximab.

For the CLL dose-escalation cohorts, one DLT was reported to date. This Grade 5 event of febrile neutropenia resulted in the patient's death. Whereas the contribution of the study drug to the neutropenia could not be completely ruled out, other factors, including bone marrow involvement of disease that resulted in baseline anemia, thrombocytopenia and neutropenia, and clinical evidence of disease progression may have also played a contributory role.

Single-Agent DCDT2980S and DCDT2980S Combined with Rituximab in NHL

Forty-nine patients received single-agent DCDT2980S at a starting dose of $\geq$ 1.8 mg/kg (7 at 1.8 mg/kg, 42 at 2.4 mg/kg); 16 patients received DCDT2980S at a starting dose of $\geq$ 1.8 mg/kg in combination with rituximab (5 at 1.8 mg/kg, 11 at 2.4 mg/kg). Overall the safety profile of DCDT2980S combined with rituximab did not differ from that of single-agent DCDT2980S.

Treatment-emergent hematologic and commonly reported nonhematologic adverse events for all grades in patients treated with single-agent DCDT2980S and DCDT2980S plus rituximab included neutropenia (29%), febrile neutropenia (3%), infection (system organ class; 43%), anemia (25%), thrombocytopenia (12%), peripheral neuropathy

(28%), diarrhea (40%), pyrexia (14%), nausea (34%), and fatigue (55%). Treatment-emergent Grade ≥ 3 adverse events included neutropenia (25%), febrile neutropenia (3%), infection (system organ class; 11%), anemia (5%), peripheral neuropathy (3%), diarrhea (5%), pyrexia (2%), and fatigue (3%). Serious adverse events assessed by the treating investigator to be related to DCDT2980S were reported in 21% of patients. Dose discontinuations for adverse events were reported in 20% of patients.

Refer to the DCDT2980S Investigator's Brochure for complete and updated details related to safety.

d. Efficacy in Non-Hodgkin's Lymphoma

Investigator-based objective responses were observed in 17 of 43 (40%) patients treated with single-agent DCDT2980S and 5 of 15 (33%) patients treated with DCDT2980S combined with rituximab. Among patients with relapsed or refractory DLBCL, 11 of 28 (39%) objective responses (5 complete responses [CR] and 6 partial responses [PR]) were observed with single-agent DCDT2980S and 3 of 7 (43%; 2 CR, 1 PR) with DCDT2980S combined with rituximab. Among patients with relapsed or refractory indolent NHL (iNHL), 6 of 13 (46%) objective responses (2 CR, 4 PR) were observed with single-agent DCDT2980S and 1 of 4 (PR) with DCDT2980S combined with rituximab.

Refer to the DCDT2980S Investigator Brochure for complete and updated details related to anti-tumor activity.

1.2.2 DCDS4501A

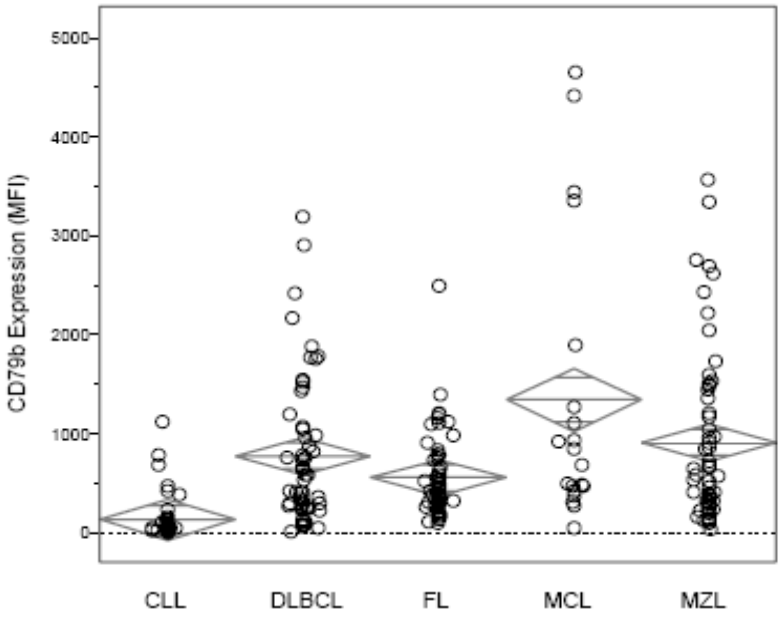
1.2.2.1 Background and Preclinical Data

CD79b is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of B cell–derived malignancies, including nearly all NHL and CLL samples tested (see Figure 2) (Dornan et al. 2009). Antibodies bound to CD79b are rapidly internalized, making CD79b ideally suited for targeted delivery of cytotoxic agents (Polson et al. 2007, 2009).

Similar to DCDT2980S, DCDS4501A is an ADC that contains a humanized immunoglobulin-G1 (IgG1) anti–human CD79b MAb (MCDS4409A) and MMAE linked through MC-VC-PABC.

Comprehensive pharmacologic, PK, PD, and toxicological evaluations were undertaken to support the entry of DCDS4501A into clinical trials. Because DCDS4501A specifically recognizes CD79b on B cells of human but not on those of cynomolgus monkey, rat, or mouse, a surrogate ADC (DCDS5017A) that binds to cynomolgus monkey CD79b was generated to assess the antigen-dependent pharmacological, toxicological, and PK/PD activities in cynomolgus monkeys. The structure, binding epitope, and binding affinity of the surrogate ADC are similar to those of DCDS4501A.

Figure 2 CD79b Expression Levels on B-Cell Tumor Cells



CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MFI = mean fluorescence intensity; MZL = marginal zone lymphoma.

CD79b expression levels (MFI) on B-cell tumor cells were assessed by flow cytometry in patients diagnosed with the following B-cell lymphomas: CLL (n = 49), DLBCL (n = 59), FL (n = 58), MCL (n = 20), and MZL (n = 60).

DCDS4501A bound human CD79b with high affinity ($K_d = 1.83 \pm 0.26$ nM); the surrogate ADC also showed similar high binding affinity to cynomolgus monkey CD79b. DCDS4501A displayed potent and selective inhibition of tumor cell proliferation in vitro ($IC_{50} = 0.071$ nM $\pm$ 0.01 nM) in cell viability assays. Moderate ADCC but no CDC activity was observed with the unconjugated clinical candidate antibody MCDS4409A. Both clinical and surrogate unconjugated antibodies showed no appreciable cytokine release when evaluated in in vitro cytokine release assays with PBMCs. Moderate elevations in interleukin (IL)-1α and interferon-inducible protein (IP)-10 were observed only with the unconjugated clinical antibody, however the clinical significance of these observations are not known because IL-1α and IP-10 are not produced by B cells, are not involved in B-cell signaling through CD79b, and are not associated with cytokine-release syndromes in vivo.

Single intravenous (IV) doses of DCDS4501A resulted in inhibition of tumor growth in murine xenograft models of lymphoma. Tumor regression was observed at doses ranging from 0.5 to 3 mg/kg. In contrast, MCDS4409A showed no activity. DCDS4501A administered at 5 mg/kg demonstrated better anti-tumor activity compared to a current standard-of-care regimen (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) in xenograft models of NHL. PD studies demonstrated that doses of the surrogate ADC ranging from 0.3 to 5 mg/kg resulted in a decrease of

peripheral blood B cells in cynomolgus monkeys. A preferential decrease of proliferating B cells ($CD20^+$ $Ki67^+$) compared to the resting B cells ($CD20^+$ $Ki67^-$)) by the surrogate ADC was demonstrated in cynomolgus monkeys, in line with the expected mechanism of action of an anti-mitotic agent, MMAE.

Due to B cell–mediated CL, non-linear pharmacokinetics were observed with the surrogate ADC in cynomolgus monkeys following single IV doses of 0.3–3 mg/kg or four doses of 3 and 5 mg/kg given Q3W. The total antibody exposure after the fourth dose increased approximately 1.2- to 1.5-fold compared to the first dose. As expected, the toxicokinetic profile of the clinical ADC in rats and cynomolgus monkeys was linear in the tested dose range. Consistent with the half-life of the clinical ADC, minimal accumulation was observed following weekly dosing in rats and no accumulation was observed following Q3W dosing in cynomolgus monkeys. The free MMAE concentrations in plasma following administration of the clinical or surrogate ADCs were generally low and overall did not exceed 2 ng/mL, regardless of dose. The overall incidence of anti-therapeutic antibodies (ATAs) was 20%–67% following administration of the clinical or surrogate ADCs in cynomolgus monkeys; however, the ATAs did not appear to impact the toxicokinetic/PK parameter estimates.

In repeat-dose toxicity studies in rats and cynomolgus monkeys, DCDS4501A and the surrogate ADC were well tolerated in monkeys up to doses of 5 mg/kg and 3 mg/kg respectively, with 3 mg/kg considered the HNSTD. In rats, DCDS4501A was well tolerated up to 6 mg/kg ($STD_{10} = 10$ mg/kg). The predominant antigen-independent findings associated with DCDS4501A or surrogate ADC exposure were reversible bone marrow toxicity and associated peripheral blood cell effects in both monkeys and rats. Administration of the surrogate ADC to monkeys also resulted in expected antigen-dependent reversible decreases in peripheral blood B cells and the disappearance of B-cell germinal centers in splenic lymphoid follicles at doses ≥ 3 mg/kg. Additional findings observed in rats but not in monkeys included thymic lymphoid depletion at ≥ 6 mg/kg, minimal to mild liver toxicities (at ≥ 6 mg/kg), lung toxicities at 10 mg/kg in male animals only, and a slight increase in apoptosis and mitoses in multiple tissues, including skin and adnexa. Hepatobiliary toxicity consisted of transient dose-dependent liver enzyme elevations accompanied by minimal to slight dose-dependent increases in mitotic figures/apoptosis in hepatocytes, sinusoidal cells, and bile duct epithelium as well as minimal to slight dose-dependent random focal hepatic necrosis. Pulmonary toxicity was characterized by minimal to slight dose-dependent alveolar macrophage infiltration, sometimes accompanied by minimal to slight type II pneumocyte hyperplasia/hypertrophy. These findings were consistent with the expected pharmacologic effect of MMAE on inducing mitotic arrest due to inhibition of tubulin polymerization. Except for two individual instances (one female given 10 mg/kg in the liver and one male given 10 mg/kg in the lung), these findings were completely reversible after a 6-week recovery period. Non-reversible male reproductive

toxicity, characterized by degeneration of testicular seminiferous tubules, was observed in rats at all doses.

Complete details of preclinical studies of DCDS4501A can be found in the DCDS4501A Investigator's Brochure.

1.2.2.2 DCDS4501A Clinical Data

a. Patient Enrollment

Both DCDS4501A monotherapy and combination therapy with rituximab are being studied in a Phase I study (Study DCS4968g) of patients with relapsed or refractory B-cell malignancies expected to express CD79b, including indolent NHL, DLBCL, MCL, and CLL.

All data presented herein is based on a data entry cutoff of 28 February 2013, with clinical data available from 60 patients with NHL (excluding patients with CLL) enrolled in dose-escalation and expansion cohorts. These include 51 patients who were treated with single-agent DCDS4501A ranging from 0.1 to 2.4 mg/kg administered intravenously every 21 days and 9 patients who were enrolled into a single Phase Ib cohort with DCDS4501A administered at a dose of 2.4 mg/kg in combination with 375 mg/m^2 rituximab.

In the CLL dose-escalation cohorts, two DLTs were reported at the single-agent dose of 1.8 mg/kg. Enrollment into the CLL cohorts was stopped on 7 January 2013. Refer to the DCDS4501A Investigator Brochure for details regarding clinical data in CLL patients.

b. Pharmacokinetics

The pharmacokinetics of DCDS4501A were characterized in the Phase I Study DCDS4501A. DCDS4501A was administered in patients with NHL at escalating doses of 0.1 to 2.4 mg/kg Q3W as monotherapy and following administration of rituximab in the Phase Ib cohort. Three analytes were quantified: acMMAE, total antibody, and free MMAE.

Preliminary PK analysis based on available data as of 22 June 2012 is summarized below. The CL estimates of acMMAE and total antibody of each dose level is in the range of 14.9–21.2 mL/day/kg and 7.12–27.9 mL/day/kg, respectively. CL estimates were similar across doses of 0.1–2.4 mg/kg tested, suggesting dose-proportional increase of acMMAE and total antibody exposure. The CL of acMMAE was faster than that of total antibody at each dose level.

The mean value of V_{ss} of acMMAE and total antibody of each dose level ranged from 61 to 80.8 mL/kg and from 59.4 to 114.3 mL/kg, respectively, across the dose levels tested, which approximated human serum volume. V_{ss} values did not appear to change substantially with dose. The half-lives for acMMAE and total antibody are from 2.4 to 5.5 days and 2.9 to 7 days, respectively.

In a single-agent dose-escalation study, for acMMAE and total antibody, the time to maximum concentration occurred immediately after infusion. For free MMAE, the time to maximum concentration was approximately 2 to 3 days after infusion. C_{max} and AUC_{inf} of free MMAE appear increased with dose across the dose levels. A half-life of 3–4 days for free MMAE was observed, which is relatively long and similar to acMMAE and suggests formation rate–limited kinetics for free MMAE. No accumulation of free MMAE is expected for the Q3W regimen. The C_{max} values of free MMAE in NHL patients were at least 100-fold lower compared with acMMAE concentrations at each dose level, suggesting a slow release of free MMAE from acMMAE and potentially fast elimination once it is formed.

Preliminary comparisons of pharmacokinetics between patients with NHL and CLL (for which patients are enrolled into separate dose-escalation cohorts) treated with identical doses of DCDS4501A provide some insight into the factors that affect pharmacokinetics. Both acMMAE and total antibody were cleared faster in CLL patients than in NHL patients. This observation is likely to be related to the high number of circulating B cells generally observed in CLL patients, which may result in significant target-mediated CL of DCDS4501A. The free MMAE exposure in CLL patients was relatively low compared with that of its parent conjugate.

To date, PK data for patients treated with DCDS4501A in combination with rituximab is limited. Consequently, full comparison with single-agent DCDS4501A pharmacokinetics is not possible. On the basis of very limited data from 3 patients, total antibody pharmacokinetics was comparable between 2.4 mg/kg of DCDS4501A administered as a single agent and following rituximab administration, suggesting that when given in combination, rituximab does not affect the pharmacokinetics of DCDS4501A; the effect of DCDS4501A on rituximab pharmacokinetics will be assessed.

All observations will be verified with additional data from the ongoing Phase I study as well as this study.

Refer to the DCDS4501A Investigator Brochure for complete and updated details.

c. Safety

Dose-Limiting Toxicities

Study DCS4968g utilizes a standard 3+3 dose escalation cohort enrollment scheme. Patients enrolled into each dose-escalation cohort in Study DCS4968g have been observed for DLTs for a minimum of 21 days after their first dose of DCDS4501A. Any patient who did not complete the DLT observation period for any reason other than a DLT was replaced.

DLT of Grade 4 neutropenia occurred in 1 patient out of 10 DLT-evaluable patients in the 2.4 mg/kg single-agent cohort and 1 patient out of 9 DLT-evaluable patients in the 2.4 mg/kg + rituximab cohort. Doses of DCDS4501A greater than 2.4 mg/kg as

monotherapy or in combination with rituximab were not assessed. Consequently, DCDS4501A at 2.4 mg/kg was therefore determined to be the RP2D as both monotherapy and in combination with rituximab.

In the CLL dose-escalation cohorts, two DLTs were reported at the single-agent dose of 1.8 mg/kg. One patient had a Grade 4 neutropenia, and 1 patient had a Grade 4 invasive fungal infection.

Single-Agent DCDS4501A and DCDS4501A Combined with Rituximab

Fifty-two patients received single-agent DCDS4501A at a starting dose of ≥ 1.8 mg/kg (6 at 1.8 mg/kg, 45 at 2.4 mg/kg); an additional 9 patients received DCDS4501A at a dose of 2.4 mg/kg in combination with rituximab. Overall, the safety profile of DCDS4501A combined with rituximab did not differ from that of single-agent DCDS4501A.

Treatment-emergent hematologic and commonly reported non-hematologic adverse events of all grades in patients treated with single-agent DCDS4501A and DCDS4501A plus rituximab included neutropenia (50%), febrile neutropenia (5%), infection (system organ class; 35%), anemia (13%), thrombocytopenia (18%), peripheral neuropathy (32%), diarrhea (43%), pyrexia (37%), nausea (35%), and fatigue (18%). Treatment-emergent Grade ≥ 3 adverse events included neutropenia (43%), febrile neutropenia (5%), infection (system organ class; 10%), anemia (8%), peripheral neuropathy (7%), diarrhea (3%), pyrexia (2%), and fatigue (5%). Serious adverse events assessed by the treating investigator to be related to DCDS4501A were reported in 20% of patients. Dose discontinuations for adverse events were reported in 33% of patients.

Refer to the DCDS4501A Investigator's Brochure for complete and updated details related to safety.

d. Efficacy

Investigator-based objective responses were observed in 28 of 49 (57%) patients treated with single-agent DCDS4501A and 7 of 9 patients (78%) treated with DCDS4501A combined with rituximab. Among patients with relapsed or refractory DLBCL, objective responses were observed in 16 of 30 (53%; 4 CR, 12 PR) patients treated with DCDS4501A; 1 patient with DLBCL was treated with DCDS4501A combined with rituximab and achieved a PR. Among patients with relapsed or refractory iNHL, objective responses were observed in 7 of 14 (50%; 2 CR, 5 PR) patients treated with single-agent DCDS4501A and 5 of 5 (100%; 2 CR, 3 PR) patients treated with DCDS4501A plus rituximab.

Refer to the DCDS4501A Investigator's Brochure for complete and updated details regarding anti-tumor activity.

1.2.3 Rituximab

Rituximab has been shown to be an effective treatment for CD20-positive B-cell malignancies and is commonly used both as a single agent and in combination with cytotoxic chemotherapy. Rituximab binds to CD20, a hydrophobic, transmembrane protein that is present on pre–B cells and mature B cells and in ≥ 90% of B-cell NHLs. It exerts its cytotoxic effects via complement-mediated B-cell lysis, ADCC, and induction of apoptosis (Cartron et al. 2004).

In the United States, rituximab has been approved by the U.S. Food and Drug Administration (FDA) for the following indications in NHL: as a single agent for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL; for the treatment of relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL, including initial treatment weekly for eight doses and re-treatment (weekly for four doses) in patients who responded to an initial course of rituximab; for the treatment of low-grade, CD20-positive B-cell NHL, in combination with cyclophosphamide, vincristine, and prednisone (CVP) induction chemotherapy in previously untreated patients with follicular, CD20-positive NHL; as treatment in previously untreated patients with low-grade, CD20-positive NHL who achieve an objective response or stable disease (SD) following CVP induction; and as maintenance therapy for previously untreated follicular CD20-positive B-cell NHL after achieving a response to a regimen including chemotherapy and rituximab.

In the European Union, rituximab (MabThera®) is approved for the treatment of the following indications in NHL: treatment of patients with Stage III–IV follicular NHL who are chemotherapy-resistant or in their second or subsequent relapse after chemotherapy; treatment of patients with CD20-positive DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy; as front-line therapy in Stage III–IV follicular NHL in combination with CVP chemotherapy; as maintenance therapy in patients with relapsed or refractory, follicular NHL responding to induction treatment with CHOP or R-CHOP; and as maintenance treatment for patients with FL who have responded to initial treatment with rituximab plus chemotherapy.

Rituximab has also been approved for the treatment of CLL. The European Medicines Agency (EMA) granted an approval for the use of rituximab in combination with chemotherapy for previously untreated CLL. The FDA approved the use of rituximab in combination with fludarabine and cyclophosphamide for patients with previously untreated and previously treated CD20-positive CLL.

Refer to the Rituximab Investigator's Brochure for complete details regarding clinical data related to approved indications. For rituximab safety information, refer to local rituximab prescribing information.

1.2.4 Obinutuzumab

1.2.4.1 Obinutuzumab Mechanism of Action

Obinutuzumab ([G], also known as RO5072759, GA101, Gazyva™, and Gazyvaro™) is a humanized type II and glycoengineered anti-CD20 MAb, derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics (Mössner et al. 2010; Golay et al. 2013):

- High-affinity binding to CD20 antigen on B cells
- Type II binding mode to the CD20 antigen, leading to a more even distribution of bound antibody to the surface membrane of the B cell due to lack of CD20 translocation into lipid rafts after antibody binding and low complement activation and low complement-dependent cytotoxicity related to the recognition of the CD20 epitope
- Compared with the type I anti-CD20 antibodies rituximab or ofatumumab, increased ADCC and antibody-dependent cell-mediated phagocytosis (ADCP) related to an improved binding of obinutuzumab to the different allotypes of FcγRIIIa and FcγRIIIb expressed by natural killer (NK) cells , monocytes/macrophages and neutrophils
- Compared with rituximab, increased direct cell-death induction related to an elbow hinge amino exchange of the Fab region and type II binding of the CD20 epitope

Obinutuzumab received FDA approval in November 2013 and EMA approval in July 2014 on the basis of the CLL-11 Study BO21004 for patients with relapsed Chronic Lymphocytic Leukemia. Obinutuzumab plus chlorambucil showed superiority over rituximab plus chlorambucil in all efficacy parameters such as overall response rate (ORR), complete remission rate (CRR), minimal residual disease (MRD), progression-free survival (PFS), event-free survival (EFS), and duration of response (DOR) (Goede et al. 2014).

Obinutuzumab is currently being explored in the treatment of lymphoid malignancies such as aggressive and indolent lymphomas (DLBCL, FL, and marginal zone lymphoma [MZL]). Preliminary data suggest possible increased anti-lymphoma efficacy over rituximab, a hypothesis that is currently being explored in several randomized trials, including a Phase III study of R-CHOP versus G-CHOP in first-line treatment of DLBCL, a Phase III study of R-chemotherapy (CHOP, CVP, or bendamustine) followed by rituximab maintenance compared with G-chemotherapy (CHOP, CVP, or bendamustine) followed by obinutuzumab maintenance in first-line treatment of FL and MZL, and a Phase III study of obinutuzumab combined with bendamustine compared with bendamustine in patients with rituximab-refractory indolent NHL.

1.2.4.2 Obinutuzumab Nonclinical Toxicology

The nonclinical toxicology of obinutuzumab has been evaluated in repeat-dose studies in cynomolgus monkeys given weekly IV (30-minute infusion) up to 26 weeks in duration and weekly SC injections for 4 weeks in duration. The high dose of 50 mg/kg in the 26-week study resulted in a steady-state area under the concentration-time curve from 0

to 24 hours (AUC_{0-24}) exposure of 341,000 μg•hr/mL, which is approximately 61-fold above that of the clinical exposure of 5584 μg•hr/mL.

Consistent with expected pharmacologic activity, obinutuzumab caused marked decreases in B cells, with corresponding lymphoid depletion in spleen and lymph nodes. Circulating CD40-positive mature B cells began to reverse after several months without treatment and maximally reversed to 7%–152% of baseline by 37 weeks. In addition, transient decreases in NK cells were observed; this finding is consistent with the pharmacologic effect of FcγRIIIa binding. Suspected opportunistic infections in as many as three unscheduled deaths were considered a possible secondary result of B-cell depletion.

Obinutuzumab was immunogenic in the cynomolgus monkey, which led to reduced systemic exposures in several animals and abrogation of the pharmacologic activity. Hypersensitivity reactions were noted that included systemic inflammation and infiltrates consistent with immune complex–mediated hypersensitivity reactions such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation and led to unscheduled termination in six animals.

Both the clinical IV formulation and the SC formulation of obinutuzumab were locally well tolerated across studies. No effects were present in male and female reproductive parameters included in the 26-week IV dose study. No obinutuzumab-related effects were observed on CNS, respiratory, or cardiovascular function.

In vitro assays using undiluted human whole blood measured significant increases in cytokine secretion caused by obinutuzumab, indicating that obinutuzumab has an increased propensity to trigger first infusion–related cytokine release in patients.

See the Obinutuzumab Investigator's Brochure for details on the nonclinical studies.

1.2.4.3 Obinutuzumab Nonclinical Efficacy

Obinutuzumab has in vivo efficacy superior to rituximab in various human lymphoma xenograft models. Both antibodies were tested in human SUDHL-4 cells (DLBCL model) injected subcutaneously in severe combined immunodeficient (SCID) beige mice. Rituximab administration was started when tumors were established and rapidly growing. Results showed that rituximab at 10 mg/kg inhibited tumor growth compared with rituximab at 1 mg/kg; however, increasing the rituximab dose to 30 mg/kg did not result in increased efficacy and rituximab was not able to achieve complete tumor regression. In contrast, obinutuzumab showed a dose-dependent increase in efficacy in the range of 1–30 mg/kg. Results showed complete tumor regression in all animals and lasting tumor eradication in 9 of 10 animals at the highest dose of 30 mg/kg and in 1 of 10 animals at a dose of 10 mg/kg.

In another experiment, SUDHL4 xenografts in SCID mice were first treated with weekly rituximab 30 mg/kg. When the tumors became refractory to rituximab (Day 35), rituximab treatment was continued or changed to either weekly vehicle control or obinutuzumab 30 mg/kg. While tumors in control- and rituximab-treated mice continued to grow, obinutuzumab-treated mice showed control of tumor growth and lived until Day 61 when control or rituximab-treated mice had already been sacrificed.

Additional studies have also shown similar results, with obinutuzumab treatment controlling tumor growth, whereas vehicle- and rituximab-treated tumors were not controlled (Mössner et al. 2010).

See the Obinutuzumab Investigator's Brochure for details on the nonclinical studies.

1.2.4.4 Obinutuzumab Clinical Experience

As of July 2013, more than 1900 patients with CD20-positive malignant disease have been treated with obinutuzumab in clinical trials. Clinical data for obinutuzumab are available from six clinical trials, including three Phase I and Phase II studies of obinutuzumab monotherapy, a Phase Ib chemotherapy combination study in NHL (Study BO21000), and two Phase III studies (Study BO21004 in CLL and Study GAO4753g in NHL).

Infusion-related reactions (IRRs), mostly Grades 1 and 2, are the most common adverse events observed during therapy. IRRs have been associated predominantly with the first infusion, generally occurring early during the infusion, shortly after the infusion, or, in some cases, up to 24 hours after the completion of the infusion. In a few patients, concurrent signs of laboratory tumor lysis syndrome (TLS) were observed. The incidence and intensity of IRRs decreased strongly with subsequent infusions of obinutuzumab. On the basis of preliminary observations, extensive tumor burden, tumor factors, and host factors may be predisposing factors for the occurrence of IRRs. The frequency and severity of IRRs is also reduced in lymphomas compared with CLL.

Other frequently observed adverse events include infections and neutropenia. Grade 3–4 thrombocytopenia and neutropenia, including febrile neutropenia, have been reported with obinutuzumab, associated predominantly with treatment of CLL rather than NHL. Given its anticipated mode of action, which results in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections during and after treatment.

Data from Study BO20999 (obinutuzumab monotherapy) showed safety and efficacy of single-agent obinutuzumab in patients with relapsed indolent and aggressive lymphomas. Responses were seen at both lower (400 mg) and higher (1600/800 mg) doses, although responses increased at the higher dose, with 54% of patients with indolent lymphoma and 32% of patients with aggressive lymphomas showing PR or CR at the end of treatment (EOT) (Morschhauser et al. 2013; Salles et al. 2013).

Study BO21000 (Phase Ib) evaluated obinutuzumab in combination with chemotherapy: obinutuzumab with fludarabine and cyclophosphamide and obinutuzumab with CHOP (Radford et al. 2013). Both chemotherapy combinations were shown to be feasible in patients with previously untreated or relapsed or refractory FL, with response rates of $>$90% for both regimens. Safety was acceptable, with no new or unexpected adverse events observed. The most common adverse event was neutropenia.

Data from obinutuzumab in combination with chlorambucil in CLL (Phase III Study BO21004) showed increased efficacy of this combination over rituximab-chlorambucil, with a hazard ratio of 0.39 for PFS. IRRs were common (65% all grades, 20% Grade 3–4, no fatal IRRs) and neutropenia occurred at increased frequency with the combination therapy (33% Grade 3–5), but there was no increase in infections or treatment-related deaths (Goede et al. 2014).

See the Obinutuzumab Investigator's Brochure for additional details on the clinical studies.

1.2.4.5 Obinutuzumab Pharmacokinetics and Pharmacodynamics

A two-compartment model comprising a time-varying CL pathway and a linear CL pathway provides an adequate description of the pharmacokinetics of obinutuzumab following IV administration in Study BO20999 and Study BO21003. Following the infusion of obinutuzumab, the elimination appears to be characterized by a linear CL pathway that is dependent on time (i.e., starting at a typical value of 630 mL/day and then gradually decreasing to an asymptote of 60 mL/day at steady state). Tumor burden may potentially contribute significantly to the CL of obinutuzumab, especially at the beginning of treatment when CD20-positive tumor cells are most abundant. As tumor burden decreases, the CL reaches an asymptote, which is considered to be primarily a function of the proteolytic metabolic CL. Some patients with a high tumor burden may appear to clear the drug from the plasma faster than patients with a low tumor burden because obinutuzumab binds to the CD20-positive tumor cells and is effectively removed from the plasma. The CL of the drug will vary with time because repeated treatments with obinutuzumab will reduce the quantity of CD20-positive tumor cells. The number of times obinutuzumab is administered during the first cycle of treatment may be expected to reduce the number of CD20-positive tumor cells, thus minimizing the impact of the time-varying CL pathway on obinutuzumab exposure.

Treatment with obinutuzumab resulted in extensive B-cell depletion, with all patients showing a reduction in B-cell counts to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before and after infusion, but transient increases occurring during the administration of obinutuzumab have been observed in the levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-10, and interferon (IFN)-γ.

1.3 RATIONALE FOR DOING THIS STUDY

The goals of this study are to continue to assess the safety, tolerability, and biologic and clinical activity of the combinations of DCDT2980S and rituximab and DCDS4501A and rituximab in two specific NHL patient populations: patients with relapsed or refractory follicular NHL and patients with relapsed or refractory DLBCL. An additional goal of this study is to assess the safety, tolerability, and potential biologic and clinical activity of DCDS4501A in combination with obinutuzumab, an anti-CD20 antibody, in the aforementioned NHL patient populations. These patients continue to have an extremely poor prognosis with no curative options available. Consequently, new therapeutic options are needed.

DCDT2980S, DCDS4501A, rituximab, and obinutuzumab each target antigens specific to B-cell malignancies including follicular NHL and DLBCL (see Figure 1 and Figure 2).

The randomized component of the Phase II study design permits an assessment of the clinical benefit provided by each of these molecules in combination with rituximab, which has established clinical activity in B-cell malignancies both as monotherapy and in combination with chemotherapy. Data from this study will help inform the feasibility of the combination regimens in earlier lines of therapy (e.g., as first-line therapy in newly diagnosed patients).

The non-randomized component of the study will further evaluate the safety and tolerability and clinical activity of DCDS4501A in combination with obinutuzumab in patients with relapsed or refractory follicular lymphoma or DLBCL and will also provide preliminary evidence as to which anti-CD20 agent, rituximab or obinutuzumab, in combination with DCDS4501A, provides a better benefit-risk profile in the target population being studied.

The feasibility of combining an ADC with rituximab has previously been tested clinically with the combination of another, different CD22-specific ADC, inotuzumab ozogamicin (CMC-544), with results suggesting that the addition of rituximab may have increased clinical activity without significant increase in toxicity over the ADC alone in patients with aggressive NHL (Fayad et al. 2006; Nam et al. 2009; Nina et al. 2010). As noted in Section 1.2.1 and Section 1.2.2, the combinations of DCDT2980S and rituximab, and DCDS4501A and rituximab have been shown to have acceptable safety in patients with relapsed or refractory NHL in the Phase I studies (Studies DCT4862g and DCS4968g).

Given the relatively poor prognosis of patients with relapsed or refractory hematologic malignancies that have failed standard therapies, the nonclinical toxicity profile associated with DCDT2980S and DCDS4501A treatment, and the clinical safety profile observed to date for both ADCs, the benefit-risk ratio of a clinical study of DCDT2980S and DCDS4501A, each combined with rituximab or obinutuzumab, is considered acceptable.

1.3.1 Rationale for Assessing ADC Dose of 1.8 mg/kg Combined with Rituximab in iNHL

On the basis of available Phase I data (see Section 1.2.1 and Section 1.2.2), both DCDT2980S and DCDS4501A as single agents and combined with rituximab have shown early signs of clinical activity in heavily pretreated patients with relapsed or refractory NHL. However, early evidence in the Phase I studies indicate that duration of study treatment may be limited by tolerability to ADC. Specifically, for both ADCs, peripheral sensory neuropathy has been identified as a known risk (see Section 3.4.3.5). Notably, 4 of 7 and 5 of 11 discontinuations for adverse events in Studies DCT4862g and DCS4968g, respectively, were the result of peripheral neuropathy.

Because of the chronic course and incurability of iNHL, treatment paradigms are increasingly emphasizing tolerability to treatment in addition to efficacy. As both DCDT2980S and DCDS4501A have shown single-agent activity at the 1.8 mg/kg dose level (Advani et al. 2012; Palanca-Wessels et al. 2012), the purpose of enrolling additional cohorts of patients with FL is to determine whether lower doses of ADC in combination with standard doses of rituximab result in improved tolerability while maintaining efficacy in FL.

In contrast to iNHL, treatment paradigms in relapsed or refractory aggressive lymphomas such as DLBCL continue to place a premium on anti-tumor activity and higher tolerance for treatment-related toxicity, given that the duration of disease control and survival are substantially shorter and that treatment options are extremely limited. Early Phase I data suggest lower rates of study treatment discontinuation for adverse events among patients with DLBCL compared with patients with iNHL. Taken together with anti-tumor activity observed to date, the benefit-risk profile of the currently tested ADC dose of 1.8 mg/kg is considered acceptable to combine with rituxminab in the treatment of patients with iNHL.

1.3.2 Rationale for Assessing DCDS4501A in Combination with Obinutuzumab in Relapsed or Refractory NHL

The development of next-generation anti-CD20–directed therapy may further enhance the efficacy of current standard regimens for NHL. Obinutuzumab, also known as RO5072759, GA101, and Gazyva™/Gazyvaro™, a novel type II and glycoengineered anti-CD20 antibody, has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). Obinutuzumab is currently being compared with rituximab in two large Phase III studies in patients with newly diagnosed DLBCL (Study BO21005) and with previously untreated iNHL, including FL (Study BO21223). Assuming these studies demonstrate greater clinical benefit with obinutuzumab- vs. rituximab-containing regimens, potentially altering the standard of care in NHL, it will be important to also assess the safety and efficacy of combining DCDS4501A with obinutuzumab-containing regimens.

The goals of the non-randomized portion of the Phase Ib study are to assess the safety, tolerability, and potential biologic and clinical activity of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in patients with relapsed or refractory follicular NHL or DLBCL. The RP2D, the Phase II dose-expansion portion of the study, will further evaluate the safety and tolerability and clinical activity of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in patients with relapsed or refractory follicular NHL or DLBCL.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objectives of this study are the following:

- To assess the safety and tolerability of the combination of DCDT2980S and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the safety and tolerability of the combination of DCDS4501A and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the safety and tolerability of the combination of DCDS4501A and obinutuzumab when administered to patients with relapsed or refractory follicular NHL or DLBCL
- To assess the anti-tumor activity of the combination of DCDT2980S and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and obinutuzumab in patients with relapsed or refractory follicular NHL and DLBCL based on ^{18}*F-fluorodeoxyglucose–positron emission tomography (^{18}F-FDG-PET; hereafter referred to as PET)/computed tomography (CT)* CR at the end of treatment according to Independent Review Committee (IRC) per Lugano 2014 response criteria

2.2 SECONDARY OBJECTIVES

2.2.1 Safety Objectives

The secondary safety objectives of this study are the following:

- To assess the incidence of antibody formation to DCDT2980S, DCDS4501A, and obinutuzumab as measured by the formation of ATAs
- To compare the safety and tolerability of the combination of DCT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab

2.2.2 Activity Objectives

The secondary activity objective for rituximab-containing arms of the study is the following:

- To compare the anti-tumor activity of the combination of DCT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab

The secondary activity objectives for obinutuzumab-containing arms of the study are the following:

- CR at end of treatment based on PET*/CT*, as determined by the investigator
- Objective response (OR; CR or PR) at end of treatment based on PET*/CT,* as determined by investigator and IRC
- CR at end of treatment based on CT only, as determined by the investigator and IRC
- OR *(CR or PR)* at end of treatment based on CT only, as determined by the investigator and IRC
- Best objective response (BOR, CR or PR) while on study based on PET*/CT* or CT only, as determined by the investigator

2.2.3 Pharmacokinetic Objectives

The PK objectives of this study are the following:

- To characterize the pharmacokinetics of DCDT2980S and rituximab in patients with relapsed or refractory NHL when the two drugs are given in combination
- To characterize the pharmacokinetics of DCDS4501A and rituximab or obinutuzumab in patients with relapsed or refractory NHL when the two drugs are given in combination

2.3 EXPLORATORY OBJECTIVES

2.3.1 Efficacy Objectives

The exploratory efficacy objectives for this study are to evaluate the long-term outcome of obinutuzumab-treated patients according to Lugano 2014 response criteria, as measured by the following:

- Duration of response based on *PET/CT* and/or CT scans*, as determined by the investigator*
- Progression-free survival (PFS) based on PET*/CT* and/or CT scans*, as determined by the investigator*
- Event-free survival (EFS) based on PET*/CT* and/or CT scans*, as determined by the investigator*
- Overall survival

2.3.2 Biomarker Objectives

The objectives of this study related to assessment of biologic markers are the following:

- To make a preliminary assessment of biologic markers that might act as predictors of DCDT2980S + rituximab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL
- To make a preliminary assessment of biologic markers that might act as predictors of DCDS4501A + rituximab or obinutuzumab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL

2.3.3 Patient-Reported Outcomes Objective

The objective of this study related to assessment of patient-reported outcomes (PRO) is the following:

- To assess patient-reported tolerability to study treatment and the impact of study treatment on patient functioning on the basis of PRO in Rituximab cohorts only

2.3.4 Crossover Treatment Objective

The objective of this study related to assessment of crossover treatment is the following:

- To preliminarily assess the safety, tolerability, and anti-tumor activity of DCDT2980S and DCDS4501A, either as a single-agent or in combination with rituximab, as crossover treatment following disease progression on initial study treatment. (Note: This objective applies only to patients enrolled in Arms A and B [see Section 3.1])

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

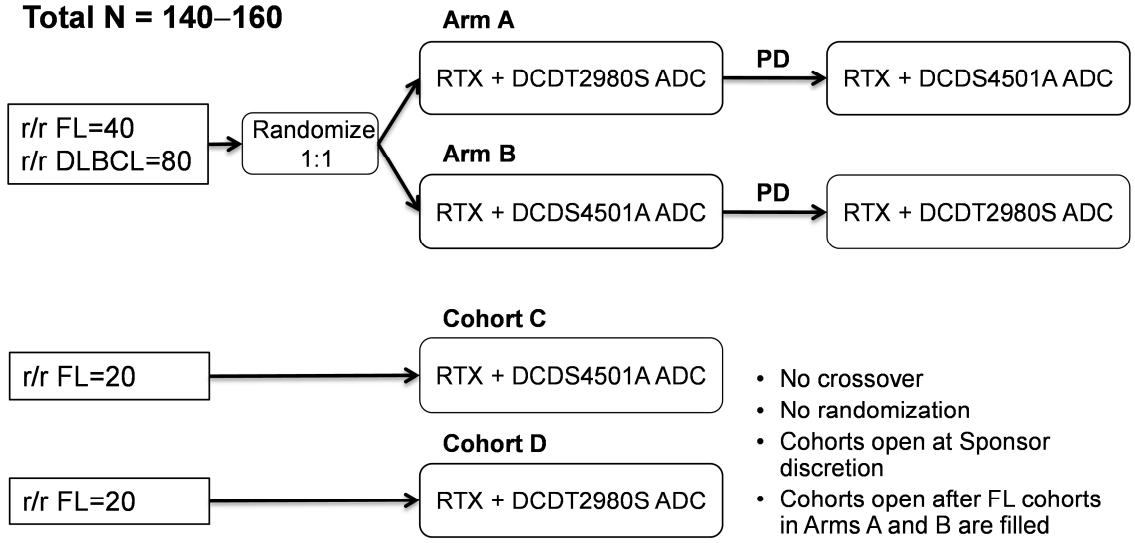
This is a Phase Ib/II, multicenter, open-label study. Up to approximately 246 patients with relapsed or refractory FL and DLBCL will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data. Arms A and B and Cohort C are no longer enrolling patients.

For Obinutuzumab Cohorts:

Only investigational sites in the United States will enroll patients into Cohort E. Investigational sites in the United States and worldwide will participate in Cohorts G and H.

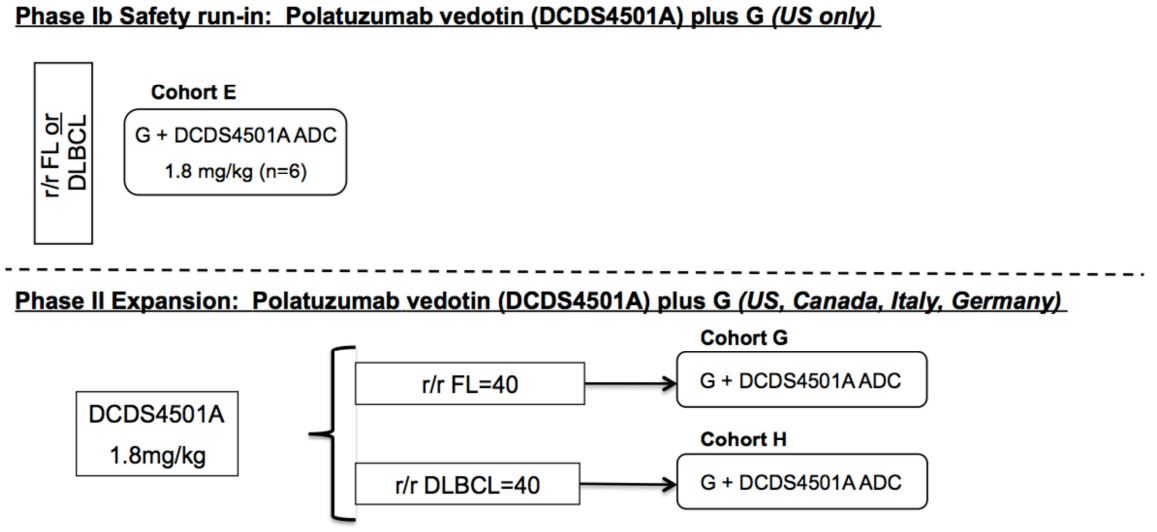
The study will be composed of a randomized portion and a non-randomized portion, as illustrated in Figure 3.

Figure 3a Study Schema for Rituximab-Containing Arms/Cohorts (Closed to Enrollment)



Arms A and B: RTX (375 mg/m^2) + ADC (2.4 mg/kg) administered in every-21-day cycles.
Cohorts C and D: RTX (375 mg/m^2) + ADC (1.8 mg/kg) administered in every-21-day cycles.

Figure 3b Study Schema for Obinutuzumab-Containing Arms/Cohorts



Cohorts E, G and H: Obinutuzumab (G) (1000 mg) D1, D8, D15 in Cycle 1, then D1 of each subsequent cycle.
Polatuzumab vedotin (DCDS4501A) (1.8 mg/kg) on D1. Cycles administered every 21 days.

ADC = antibody-drug conjugate; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; G = GA101/obinutuzumab; PD = progressive disease; r/r = relapsed or refractory; RTX = rituximab.

3.1.1 Rituximab-Containing Regimens with DCDT2980S or DCDS4501A

3.1.1.1 Randomized Portion of the Study (Arms A and B) – Closed to Enrollment

Following determination of eligibility, patients within each disease group will be randomized in a 1:1 ratio to receive one of two treatments:

- Arm A: Rituximab (375 mg/m^2) followed by DCDT2980S (2.4 mg/kg) every 21 days;
- Arm B: Rituximab (375 mg/m^2) followed by DCDS4501A (2.4 mg/kg) every 21 days

The first day of treatment constitutes Day 1 of each cycle. A typical cycle is 21 days in duration.

A dynamic hierarchical randomization scheme will be employed with respect to the following stratification factors:

- For patients with FL (see Section 3.1.4 for definitions)

  Rituximab refractory disease (no response or disease relapse $<$6 months from last rituximab treatment) versus rituximab relapsed disease (disease relapse after response $\geq$ 6 months from last rituximab treatment)

- For patients with DLBCL (see Section 3.1.5 for definitions)

  Second-line versus third-line (or beyond) therapy

  For second-line patients, disease relapse or no objective response (CR, unconfirmed CR [CRu], or PR) <12 months from the start of initial therapy versus disease relapse, after initial objective response (CR, unconfirmed response [CRu] or PR), $\geq$ 12 months from start of initial therapy

  For third-line patients, failure to achieve a CR or progression < 6 months from start of most recent therapy versus CR or progression ≥ 6 months from start of most recent therapy

No formal testing comparing the two treatment arms in the randomized portion of the study is planned.

3.1.1.2 Non-Randomized Portion of the Study with Rituximab (Cohorts C and D)– Closed to Enrollment

Only select investigator sites that have agreed to participate in the non-randomized portion of the study will enroll patients into these cohorts.

Patients with relapsed or refractory follicular NHL will be enrolled in Cohorts C and D to receive rituximab (375 mg/m2) combined with DCDT2980S or DCDS4501A at a dose of 1.8 mg/kg. The first day of treatment constitutes Day 1 of each cycle. A typical cycle will be 21 days in duration.

The opening of either or both cohorts will be at the Sponsor's discretion and only after the enrollment of patients with FL into the randomized portion of the study is completed. Patients will not be randomized to receive one treatment or the other. It is anticipated that Cohort C and D will be opened sequentially.

3.1.2 All Patients on Rituximab-Containing Arms/Cohorts

All patients on rituximab-containing regimens, regardless of assigned arm/cohort, will receive DCDT2980S or DCDS4501A and rituximab administered by IV infusion on a 21-day cycle. For the first two cycles, rituximab will be administered by IV infusion on Day 1 and DCDT2980S or DCDS4501A will be administered by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this instance, rituximab will be administered first, followed by DCDT2980S or DCDS4501A. In certain circumstances—for example, IRRs requiring interruption or slowing of infusion rate—rituximab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDT2980S or DCDS4501A may be administered on Day 2 following completion of the rituximab infusion or on Day 3 of the cycle.

Patients may receive treatments for up to 1 year (17 cycles on an every-21-day schedule) if not discontinued because of significant toxicity, disease progression, or withdrawal from study.

Patients will be evaluated for safety and efficacy according to the Schedules of Assessments outlined in Appendices A-1, A-2, and A-4. Initial response assessments in this study will be performed every 3 months from the initiation of therapy until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). Additional response assessments for patients who proceed to crossover treatment (see Section 3.1.6) will be performed as described in Appendix A-2; response assessments for patients who discontinue study treatment (both initially assigned treatment and crossover treatment) for reasons other than disease progression will be performed as described in Appendix A-4.

Responses to study treatment will be based on investigator assessments. In addition, tumor assessment data will be transmitted to an Independent Review Facility (IRF) for collection and possible independent review.

3.1.3 Obinutuzumab-Containing Regimen with DCDS4501A (Cohorts E, G, and H)

DCDS4501A at 1.8 mg/kg will be given in combination with obinutuzumab to patients with relapsed or refractory follicular NHL and DLBCL in two stages: (1) safety run-in and (2) expansion.

Study treatment will be given in 21-day cycles for both follicular NHL and DLBCL. Patients will be treated for up to a total of 8 cycles. For the first cycle, obinutuzumab will be administered by IV infusion on Days 1, 8, and 15. DCDS4501A will be given on Day 2 for Cycle 1. In the absence of any infusion-related adverse events, obinutuzumab and DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the second cycle. If obinutuzumab and DCDS4501A are administered on the same day, the study drugs will be given sequentially. Obinutuzumab will be administered first, followed by DCDS4501A. In certain circumstances—for example, IRRs requiring interruption or slowing of infusion rate—obinutuzumab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDS4501A may be administered on Day 2 following completion of the obinutuzumab infusion.

3.1.3.1 Obinutuzumab-Containing Regimen in Phase Ib: Safety Run-In (Cohort E)

This portion of the study will consist of a safety run-in that will evaluate the safety of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in 6 patients (Cohort E). The safety run-in is described in detail in Section 3.4.

Obinutuzumab-Containing Regimens in Phase II: Expansion Stage (Cohorts G and H)

After the safety run-in has demonstrated that DCDS4501A at 1.8 mg/kg in combination with obinutuzumab is safe to administer, patients will be enrolled into two expansion cohorts based on histology of follicular NHL or DLBCL (Cohorts G and H, respectively). Forty patients will be enrolled into each expansion cohort. An additional cohort(s) may be added in the future.

3.1.4 Follicular NHL Patients for Rituximab-Containing Arms/Cohorts

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed as documented history of response (CR, CRu, or PR) of $\geq$6 months in duration from completion of all prior rituximab-containing regimens. A rituximab-containing regimen is defined as rituximab as a single agent during induction and/or maintenance or in combination with other agents during induction and/or maintenance.
- Refractory to any prior regimen containing rituximab, defined as no response to or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:

  Patients with progressive disease while receiving rituximab monotherapy, rituximab combined with chemotherapy, or rituximab maintenance therapy; patients must have received at least one full dose (375 mg/m^2) of rituximab.

Patients with no objective response (PR or CR) to a rituximab-containing regimen consisting of at least 4 weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Patients with disease relapse, after having achieved an objective response, within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Enrollment of patients with refractory disease as defined above may be limited to no greater than 60% of the total follicular NHL cohort, in order to avoid overrepresentation of the refractory disease population.

3.1.5 Follicular NHL Patients for Obinutuzumab-Containing Cohorts

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed to prior regimen(s) after having a documented history of response (CR, CRu, or PR) of $\geq$6 months in duration from completion of regimen(s)
- Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy

3.1.6 DLBCL Patients for Rituximab-Containing Arms/Cohorts

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/stem cell transplant (SCT) will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) $<$ 12 months from start of initial therapy (second-line refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response $\geq$12 months from start of initial therapy (second-line relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) $<$6 months from start of prior therapy (third-line + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response $\geq$6 months from start of prior therapy (third-line + relapsed)

Enrollment into any of the above four categories may be limited to no greater than 40% of the DLBCL cohort—and to no more than 60% of the two refractory categories combined—in order to avoid overrepresentation of any specific subpopulation, refractory patients in particular.

3.1.7 DLBCL Patients for Obinutuzumab-Containing Cohorts

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/SCT will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) $<$ 12 months from start of initial therapy (second-line refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response $\geq$ 12 months from start of initial therapy (second-line relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) $<$ 6 months from start of prior therapy (third-line + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response $\geq$ 6 months from start of prior therapy (third-line + relapsed)

3.1.8 Crossover Treatment (Randomized Patients in Arms A and B Only)

Patients randomized to Arm A or Arm B who develop progressive disease may be eligible to receive crossover treatment consisting of rituximab and the other ADC or the other ADC alone—for example, Arm B treatment for patients who have disease progression while receiving Arm A treatment, and vice versa—provided the following conditions are met:

- Patients must not have experienced a toxicity requiring the discontinuation of DCDT2980S/DCDS4501A treatment OR experienced toxicity during the last dose of study treatment that would preclude treatment with the crossover regimen.

  Patients who had modifications to dosing and/or schedule on the initial study treatment will be permitted to receive crossover treatment in the absence of toxicities on the modified dose and/or schedule. The dose and schedule of crossover treatment will be determined by the investigator and the Medical Monitor.

  Patients who had rituximab discontinued and continued on single-agent DCDT2980S/DCDS4501A treatment may receive crossover treatment of single-agent DCDS4501A/ DCDT2980S.
- Patients must have radiographically documented disease progression.
- Patients must meet all inclusion and exclusion criteria described in Section 4.1.1 and Section 4.1.2, except for those related to prior rituximab treatment.
- Acceptable toxicity: All study drug–related adverse events from the initial study treatment must have decreased to Grade 1 or baseline grade on or before the first day of treatment on the crossover regimen. Exceptions may be allowed after a careful assessment and discussion of the benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.

- Administration of crossover treatment must be in the best interests of the patient as determined after a careful assessment and discussion of benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.
- A tumor biopsy (see Section 4.5.1.9) will be required for patients with safely accessible site of disease, defined as requiring only local anesthesia and, in general, excluding the brain, lungs or any internal organs that may subject patients to significant risk.

    Patients for whom a safely accessible site of disease is not present may still receive crossover treatment without undergoing a biopsy. Eligibility to receive crossover treatment should be discussed with and approved by the Medical Monitor.

    A tumor biopsy of a safely accessible site of disease is optional for patients who are not eligible for study cross over.

Patients who are determined to be eligible for study cross over will be treated as follows:

- Assessments obtained at the initial study treatment discontinuation visit (see Section 4.5.4) may be used as screening assessments for crossover treatment. The following re-screening assessments must be repeated/obtained within 1 week prior to starting treatment on the crossover regimen, in order to re-establish baseline pretreatment clinical and disease status: targeted physical exam, Eastern Cooperative Oncology Group (ECOG) status, and hematology and serum chemistry laboratory tests.

    Re-screening tests for hepatitis B and C do not need to be performed unless there is clinical suspicion of hepatitis B and/or C positivity.

    A radiographic tumor assessment must also be performed, unless already done to document disease progression, within 6 weeks prior to starting crossover treatment.
- Crossover treatment will begin no later than 42 days after the last dose of the prior study treatment.

Patients will be treated with the crossover treatment until a second disease progression event relative to the tumor assessment, documenting progressive disease on the initial study treatment, clinical deterioration, and/or intolerance to the crossover treatment for up to a maximum of 1 year (17 cycles on an every-21-day schedule). Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in Appendices A-2. Response assessments for patients who discontinue study treatment for reasons other than disease progression will be performed as described in Appendix A-4.

Clinical data and exploratory data derived from tumor biopsies obtained prior to crossover treatment will be monitored on an ongoing basis. Genentech has the right to restrict or suspend enrollment into crossover treatment at any time. Reasons for this may include, but are not limited to, the following:

- The incidence or severity of adverse events during crossover treatment indicates a potential safety hazard to patients.
- Patient enrollment into crossover treatment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Patients who are enrolled into the non-randomized portion of the study (Cohorts C, D, E, G, and H) will not have the option to receive crossover treatment upon disease progression (see Section 3.2 for rationale).

3.2 RATIONALE FOR STUDY DESIGN

The primary rationale for the randomized non-comparative portion of the study is to assess clinical activity for the ADCs DCDT2980S and DCDS4501A in patients with relapsed or refractory NHL. The study design ensures that the patient populations under study are balanced with respect to critical variables such as prior therapy and ensures consistent clinical assessment of safety and efficacy. The collection and assessment of tumor tissue obtained prior to first study treatment and following progressive disease will provide further understanding of disease biology, possible mechanisms of resistance to the study treatment, and initial insights into tumor subtypes based on tumor biomarkers that are sensitive to study treatment. Finally, the inclusion of study treatment crossover (see Section 3.1.8) will address important questions regarding efficacy and tolerability of a second ADC-rituximab combination following disease progression on the initial ADC-rituximab combination.

The primary rationale for the non-randomized portion of the study (Cohorts C and D) is to assess the therapeutic index (i.e., the balance of efficacy and tolerability of DCDT2980S and DCDS4501A at a dose of 1.8 mg/kg in patients with relapsed or refractory follicular NHL). An informal comparison between patients with follicular NHL treated at the two doses of the ADC will help determine if tolerability is improved at the lower ADC dose without substantial compromise of efficacy.

The clinical feasibility of an ADC-rituximab combination regimen in patients with relapsed or refractory NHL has been previously studied. Results from studies of rituximab in combination with a different CD22-specific ADC, inotuzumab ozogamicin, demonstrated that when combined with rituximab, the ADC was able to be given at the single-agent MTD without the need for dose reduction of the ADC because of the lack of significant overlapping toxicity (Fayad et al. 2006; Nam et al. 2009; Nina et al. 2010).

DCDT2980S and DCDS4501A were both evaluated as single agents and in combination with rituximab in the Phase I studies Study DCT4862g and Study DCS4968g, respectively. Results from these trials have determined an MTD of 2.4 mg/kg for

single-agent DCDT2980S and an RP2D of 2.4 mg/kg for single-agent DCDS4501A in patients with mixed NHL. In addition, the RP2D of DCT2980S and DCDS4501 each in combination with rituximab (375 mg/m2) on an every-21-day schedule was determined to be 2.4 mg/kg.

Study GO27834 will continue to assess the cumulative safety and longer-term tolerability of ADC-rituximab combination therapy. Due to additional information about the benefit-risk profile of DCDS4501A at the 2.4 mg/kg dose, the Sponsor is no longer pursuing the 2.4 mg/kg dose of DCDS4501A in the obinutuzumab-containing cohorts.

The primary rationale for the non-randomized Phase Ib/II obinutuzumab-containing cohorts (Cohorts E–H) is to assess safety and clinical activity for the combination of obinutuzumab and DCDS4501A in patients with relapsed/refractory NHL (Cohorts E, G, and H). Obinutuzumab (also known as RO5072759, GA101 and Gazyva™/Gazyvaro™), a novel type II and glycoengineered anti-CD20 antibody, has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). Obinutuzumab is currently being compared with rituximab in two large Phase III studies in patients with newly diagnosed DLBCL (Study BO21005) and previously untreated iNHL, including FL (Study BO21223). Assuming these studies demonstrate greater clinical benefit with obinutuzumab- vs. rituximab-containing regimens, potentially altering the standard of care in NHL, it will be important to also assess the safety and efficacy of combining DCDS4501A with obinutuzumab-containing regimens.

Study drug dosing will occur on Days 1 or 2 of each 21-day (or 28-day) cycle to allow for recovery from potential bone marrow toxicity.

3.2.1 Rationale for the PK Sample Schedule

PK data obtained in this study will be important in informing potential future trials with this combination. Given the likely changing effect of peripheral B-cell counts, tumor burden, and target antigen expression on target-mediated drug CL over multiple doses of DCDT2980S or DCDS4501A plus rituximab or obinutuzumab when the two drugs are given in combination, the drug levels of DCDT2980S or DCDS4501A-related analytes and rituximab or obinutuzumab will be assessed in this combination study.

In Studies DCT4862g and DCS4968g, single-agent DCDT2980S and DCDS4501A administered by IV infusion every 21 days were evaluated at doses ranging from 0.1 to 3.2 mg/kg for DCDT2980S and 0.1 mg/kg to 2.4 mg/kg for DCDS4501A in patients with NHL. Intensive PK sampling of all patients in the ongoing Phase I studies will provide sufficient data to allow complete profiling of the distribution and elimination phases for DCDT2980S and DCDS4501A and the investigation of potential correlations between various PK parameters and efficacy and/or toxicity. Consequently a reduced PK sampling scheme of DCDT2980S and DCDS4501A will be used in this study.

The PK data collected in this study will allow further characterization of the PK properties of DCDT2980S and DCDS4501A. In addition, the DCDT2980S and DCDS4501A concentration results from this study will be compared with available data from the single-agent clinical studies to evaluate whether concurrent administration of rituximab affects the exposure of DCDT2980S and/or DCDS4501A.

Rituximab serum concentration measurements from this study will be compared with PK data from historical rituximab clinical studies to evaluate whether the combination with DCDT2980S and/or DCDS4501A affects the pharmacokinetics of rituximab.

Limited sampling of serum concentrations of obinutuzumab will be assessed and compared with historical data to evaluate potential PK interactions with DCDS4501A.

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety and tolerability of the combination of DCDT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab will be assessed using the following safety outcome measures:

- Incidence, nature, and severity of adverse events
- Incidence of anti-DCDT2980S, anti-DCDS4501A, or anti-obinutuzumab antibodies
- Changes in vital signs
- Changes in laboratory values

3.3.2 Pharmacokinetic/Pharmacodynamic Outcome Measures

The following PK parameters will be derived from the serum concentration–time profiles of total antibody (the sum of conjugated and unconjugated antibody), including rituximab or obinutuzumab, and plasma concentration-time profiles of acMMAE and free MMAE following administration of DCDT2980S or DCDS4501A, when appropriate, as data allow:

- Total exposure (area under the concentration-time curve [AUC])
- Maximum plasma and serum concentration (C_{max})
- CL
- Terminal half-life ($t_{1/2}$)
- V_{ss}

Compartmental, non-compartmental, and/or population methods may be used. Other parameters, such as accumulation ratio and trough plasma and serum concentration (C_{min}), may also be calculated.

The following PD outcome measures will be assessed when appropriate, as data allow:

- Peripheral blood B-cell depletion and recovery. For each visit at which $CD19^+$ B-cell measurements are taken, B-cell data will be listed for each patient by dose level as follows:

  Absolute blood cell counts

  Percent change relative to the baseline blood counts

  $CD19^+$ B-cell recovery, defined as the timepoint when the values return to baseline levels or $\geq$ 50% of baseline levels

- Assessment of the kinetics of circulating tumor DNA

3.3.3 Activity Outcome Measures

The following activity outcome measures will be assessed for rituximab-containing arms/cohorts (Arms A and B, Cohort C):

- Objective response, defined as a PR or CR
- Duration of objective response, defined as the duration of time from the first occurrence of a documented objective response to time of relapse or death from any cause
- PFS, defined as the duration from randomization to the first occurrence of progression or death within 30 days of the last administration of study drug, whichever occurs first
- OS, defined as the duration from the date of randomization/enrollment to the date of death from any cause

Objective response and disease progression will be determined using standard criteria for NHL (Cheson et al. 2007, 2014; see Appendix C-1 and Appendix C-2).

The following activity outcome measures will be assessed for obinutuzumab-containing cohorts (Cohorts E, G, and H) according to Lugano 2014 Response Criteria (Cheson et al. 2014):

The primary activity outcome measure will be assessed by:

- CR at end of treatment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) based on PET/CT, as determined by the IRC

The following secondary efficacy outcome measures will be assessed:

- OR (CR or PR) at end of treatment based on PET/CT, as determined by the investigator and IRC
- CR at end of treatment based on CT only, as determined by the investigator and IRC

- OR (CR or PR) at end of treatment based on CT only, as determined by the investigator and IRC
- BOR (CR or PR) while on study based on PET/CT or CT only, as determined by the investigator

3.3.4 Exploratory Outcome Measures

The exploratory outcome measures will include, but will not be limited to, the following:

- Confirmation and quantitation of CD22, CD79b, and CD20 expression levels in either archival or freshly obtained (when available) tumor specimens (tumor biopsies, bone marrow biopsies, peripheral blood) by immunohistochemistry/flow cytometry/quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)
- Additional assessments related to the understanding of the mechanism of action of DCDT2980S, DCDS4501A, rituximab, and obinutuzumab, e.g., assessment of circulating tumor DNA(ctDNA) to monitor response, mechanisms of resistance to DCDT2980S, DCDS4501A, rituximab, and obinutuzumab, and/or NHL pathogenesis may be included.
- Treatment and disease symptom assessments using the M.D. Anderson Symptom Inventory (MDASI) in rituximab-containing cohorts only

The following exploratory efficacy outcome measures will be assessed:

- DOR, defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse, or death from any cause, for the subgroup of patients with a best overall response of CR or PR, based on PET/CT and/or CT scans as determined by the investigator assessment. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the DOR will be censored on the date of last disease assessment.
- PFS, defined as the time from date of randomization or first treatment (for G-containing arms) to the first occurrence of progression or relapse, or death from any cause , based on PET/CT and/or CT scans as determined by the investigator assessment.
- EFS, defined as the time from date of randomization or first treatment (for G-containing arms) to any treatment failure including disease progression relapse, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first, based on PET/CT and/or CT scans as determined by the investigator assessment
- OS, defined as the time from the date of first treatment to the date of death from any cause

3.4 SAFETY PLAN

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

Safety will be evaluated through the monitoring of the following:

- Serious adverse events that are attributed to protocol-mandated interventions from the time of signing of the Informed Consent Form until the first dose of study treatment on Cycle 1, Day 1
- All adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab, whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab, whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab, whichever is later, including doses that were administered as part of crossover treatment, and which are judged to be caused by DCDT2980S, DCDS4501A, rituximab, or obinutuzumab, regardless of time of onset
- Measurements of protocol-specified hematology and clinical chemistry laboratory values
- Measurements of protocol-specified vital signs
- Assessment of ECGs
- Assessment of physical findings on clinical physical examinations

Patients who have an ongoing study drug–related adverse event will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, it is determined that the study treatment or participation is not the cause of the adverse event, or the study is terminated.

See Section 5.2.3 for assessment of causality for adverse events.

3.4.1 Safety Run-In Analysis

As outlined in Figure 3b and Section 3.1.3.1, a safety run-in analysis (Cohort E) will be conducted by the Internal Monitoring Committee (IMC) to evaluate the combination of DCDS4501A at a dose of 1.8 mg/kg with obinutuzumab. This analysis will include data from the first 6 patients treated through the safety observation period, from Cycle 1 Day 1 to Cycle 2 Day 1 for a minimum of 21days. Three patients will initially be enrolled, and then an additional 3 patients will be enrolled after the first 3 patients have safely completed the first cycle. The decision to enroll an additional 3 patients will be made by the Sponsor's Medical Monitor in consultation with the safety science leader, biostatistician, and participating investigators. At the IMC's discretion, and at any point during enrollment of the safety run-in, a decision could be made that more than 6 patients are needed to evaluate safety. Additional patients may also be enrolled at dose levels below 1.8 mg/kg of DCDS4501A (i.e., 1.4 mg/kg) based upon review of all safety data.

Safety summaries will be assessed at the safety run-in for SAEs; Grade 3-5 treatment-related AEs; all AEs; all Grade 3-5 AEs; and AEs leading to treatment discontinuation or dose modification/interruption.

- During the 6-patient safety run-in, if any patient experiences a treatment-related death, then the obinutuzumab-containing portion of the study will be closed to further recruitment.
- During the 6-patient safety run-in:

  If 2 or more of the first 3 patients enrolled experience Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment

  If 1 of the first 3 patients enrolled experiences Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then an additional 3 patients will be recruited. If 2 or more of these first 3 patients experience Grade 4 febrile neutropenia or serious (i.e., SAE) infection with Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment.

  If 2 or more of the first 6 patients to be enrolled experiences Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment.

  Before the expansion portion of the study can begin (enrollment of Cohorts G and H), six patients must have completed the safety observation period (Cycle 1 Day 1 to Cycle 2 Day 1 for a minimum of 21 days) in the safety run-in (Cohort E).

3.4.2 Internal Monitoring Committee

This study will employ an Internal Monitoring Committee (IMC). The purpose of the IMC will be to make recommendations regarding study conduct on the basis of trial safety data to ensure patient safety while receiving study treatment.

The IMC will include the Roche/Genentech Medical Monitor, at least one other Clinical Science representative who is not directly involved in the study, a Drug Safety Scientist, a biostatistician, and a statistical programmer. Representatives from other Sponsor functional areas may be included as additional ad hoc members. In addition to the ongoing assessment of the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities by the Investigator and the Medical Monitor, the IMC will review the aforementioned data at least twice during the study.

Throughout the course of the study, the IMC will meet at regular intervals during the study and at the request of the Medical Monitor (e.g., on the basis of unexpected safety signals). The IMC may make recommendations regarding study conduct, including, but not limited to, performing additional safety analyses, amending the study protocol, holding patient enrollment to one or both treatment arms pending further safety evaluations, holding/discontinuing study treatment, or terminating the study.

Specific operational details such as the committee's composition, frequency and timing of meetings and members' roles and responsibilities will be detailed in the IMC charter.

For Arms A and B: The first planned review will occur after approximately 10 patients are randomized and have at least 6 weeks follow-up, and the next formal review will occur when approximately 60 patients are randomized and have at least 6 weeks follow-up.

3.4.3 Risks Associated with DCDT2980S and DCDS4501A

The clinical safety profile of DCDT2980S and DCDS4501A based on clinical data obtained in the ongoing Phase I studies are summarized in Section 1.2.1.2 and Section 1.2.2.2. Known and suspected risks, based on clinical data to date, are described below. Guidelines regarding the management of these risks through dose and schedule modifications are described in Section 4.3.1.3 and Section 4.3.1.4.

Refer also to the Investigator's Brochure for complete and updated details.

3.4.3.1 Infusion-Related Events

Some MAbs may be associated with the development of allergic or anaphylactic reactions, to either the active protein or excipients. True allergic or anaphylactic reactions are rare after the first dose of a product, as they require prior sensitization. Patients with true allergic or anaphylactic reactions should not receive further doses of the product.

MAbs may also be associated with reactions that are clinically indistinguishable from true allergic or anaphylactic reactions but are mediated through direct release of cytokines or other pro-inflammatory mediators. Such reactions are often termed IRRs. IRRs typically occur with the first infusion of a MAb product and are generally less frequent and/or less severe with subsequent infusions. They can often be managed by slowing the infusion rate and/or pre-treatment with various medications.

Allergic or anaphylactic reactions and IRRs typically begin during or within several hours of completing the infusion. The onset of symptoms may be rapid, and some reactions may be life threatening.

Patients should be monitored for these types of reactions during and after receiving DCDT2908S and DCDS4501A. DCDT2980S and DCDS4501A should be administered

in an environment under close supervision of a physician and where full resuscitation facilities are immediately available. Specific guidelines for additional precautions to be taken during and following DCDT2980S and DCDS4501A administration are provided in Section 4.3.1.5.

3.4.3.2 Tumor Lysis Syndrome

There is a potential risk of TLS if treatment with DCDT2980S or DCDS4501A results in the rapid destruction of a large number of tumor cells. If any evidence of this occurs during the study, TLS prophylaxis measures will be instituted. Patients who are considered to have a high tumor burden (e.g., lymphocyte count $\geq 25 \times 10^9$/L) or bulky lymphadenopathy and who are considered to be at risk for TLS by the investigator will receive TLS prophylaxis (e.g., allopurinol ≥ 300 mg/day orally or a suitable alternative treatment according to institutional practice starting 12–24 hours prior to study treatment) and must be well hydrated prior to the initiation of study treatment at Cycle 1, Day 1. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion as deemed appropriate by the investigator.

3.4.3.3 Bone Marrow Toxicity/Neutropenia

Based on preclinical toxicity studies in rats and cynomolgus monkeys and clinical data from the ongoing Phase I Studies DCT4862g and DCS4968g, neutropenia has been identified as a known risk (adverse drug reaction) of both DCDT2908S and DCDS4501A. Neutropenia and neutropenia-associated events were reversible but in some cases resulted in protocol-mandated dose reductions and/or delays.

Adequate hematologic function should be confirmed before initiation of study treatment. Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Study treatment may be delayed or modified due to hematologic toxicities, as described in Section 4.3.1.

The use of G-CSF for neutropenia is described in Section 4.3.1.6. Transfusion support for anemia and thrombocytopenia is also permitted at the discretion of the treating physician.

Febrile neutropenia is commonly associated with myelotoxicity, which is considered a class effect of MMAE because it is commonly reported with ADCETRIS®, other similar ADCs, and vincristine sulfate.

Clinical data show that among the most common SAEs reported in both DCS4968g and DCT4862g studies were febrile neutropenia and pyrexia.

3.4.3.4 Immunogenicity

As expected with any recombinant antibody, DCDT2980S, DCDS4501A, and obinutuzumab may elicit an immune response and patients may develop antibodies

against DCDT2980S, DCDS4501A, or obinutuzumab. Patients will be closely monitored for any potential immune response to DCDT2980S, DCDS4501A, and obinutuzumab. Appropriate screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with DCDT2980S, DCDS4501A, and obinutuzumab. Considering the historically low immunogenicity rate of rituximab in NHL patients, ATAs against rituximab will not be monitored in this study.

3.4.3.5 Peripheral Neuropathy

On the basis of clinical data from the ongoing Phase I Studies DCT4862g and DCS4968g and data from brentuximab vedotin studies, an anti-CD30-vc-MMAE ADC (see Section 3.4.2), peripheral neuropathy (sensory and motor) has been identified as a known risk (adverse drug reaction) for both DCDT2980S and DCDS4501A.

Careful clinical evaluation of patients for neuropathy should be conducted prior to initiation of study drug. Patients should be monitored for signs of peripheral neuropathy or worsening neuropathy and appropriate action taken per protocol guidelines. Study treatment dose and schedule modifications for significant and prolonged neuropathic toxicity and dose-reduction are described in Section 4.3.1.7.

3.4.3.6 Reproductive Toxicity

Adverse effects on human reproduction and fertility are anticipated with the administration of DCDT2980S and DCDS4501A, given the mechanism of action of MMAE. Standard exclusion criteria will be used to ensure that patients of childbearing potential (male or female) are using adequate contraceptive methods.

3.4.3.7 Hyperglycemia

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other ADCs using the same vc-MMAE platform. Several patients given both DCDT2980S and DCDS4501A had abnormal fasting blood sugar (FBS) at screening with elevations of glucose following steroid administration prior to rituximab dose. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of anti-hyperglycemic medications. Emerging data suggest that hyperglycemia may occur more commonly in individuals with abnormal FBS values or known diabetes. This is also reported for ADCETRIS® (2013 SmPC and 2013 USPI).

3.4.3.8 Hepatotoxicity

Elevations in transaminase and/or bilirubin levels requiring dose modifications and treatment discontinuations have been reported in the ongoing clinical studies.

3.4.3.9 Commonly Reported Side Effects

Other commonly reported side effects of both DCDT2980S or DCDS4501A in the Phase I clinical trials and within this study include fatigue, nausea, decreased appetite, vomiting, hair thinning or loss, joint pains, loss of appetite, diarrhea, muscle aches, constipation, increases in blood glucose, and headaches.

3.4.4 Risks Associated with Rituximab Therapy and Their Management

3.4.4.1 Infusion Reactions

In single-agent clinical trials of rituximab and in post-marketing surveillance studies, mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first rituximab infusion. Other frequent infusion reaction signs and symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30–120 minutes of beginning the first infusion, and they resolved with slowing or interruption of the rituximab infusion and with supportive care (diphenhydramine, acetaminophen/paracetamol, IV saline, meperidine, and vasopressors). The incidence of infusion reactions was highest during the first infusion and decreased with each subsequent infusion.

Rituximab has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with a time to onset of 30–120 minutes. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm and may require interruption of rituximab administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events (see Appendix D). Approximately 80% of fatal infusion reactions occurred in association with the first infusion of rituximab. Because of this, patients should receive premedication with acetaminophen/paracetamol, antihistamines, or corticosteroids, in accordance with standard clinical practice, prior to rituximab infusions.

3.4.4.2 Management of Severe Infusion Reactions

Administration of rituximab will occur in a setting with emergency equipment and staff who are trained to monitor for and respond to medical emergencies. The rituximab infusion should be interrupted for severe reactions on the basis of clinical judgment.

Medications and supportive care measures—including, but not limited to, epinephrine, antihistamines, glucocorticoids, IV fluids, vasopressors, oxygen, bronchodilators and acetaminophen/paracetamol—should be available for immediate use and instituted as medically indicated for use in the event of a reaction during administration.

In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during all rituximab infusions include those with preexisting cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events, and those with high numbers of circulating malignant cells ($\geq$25,000/μL) with or without evidence of high tumor burden.

3.4.4.3 Tumor Lysis Syndrome

Rapid reductions in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia have been reported within 12–24 hours after the first infusion of rituximab. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with rituximab. The risks of TLS appear to be greater in patients with high tumor burden. Patients deemed to be at high risk for TLS complications may, at the investigator's discretion, receive their initial dose of rituximab over 2 consecutive days (see Section 4.3.2.3). Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of TLS complications, rituximab has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

3.4.4.4 Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported for some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately 1 month after the last dose of rituximab. Patients with serologic findings consistent with chronic HBV (hepatitis B surface antigen [HBsAg] positivity) or hepatitis C virus (HCV) infection (HCV RNA or antibody positivity) are ineligible for this study. Patients who are not chronically infected with HBV but have serologic evidence of prior infection at baseline (IgG hepatitis B core antibody[anti-HBc] positive but HBV DNA negative) may be eligible (if believed to be in the patient's best interest by the investigator and Medical Monitor) and would be monitored closely for perturbations in liver function during the period of rituximab treatment and every 2–4 weeks thereafter. Such patients would also be required to receive prophylactic anti-viral therapy with lamivudine for at least 6 months after completion of rituximab therapy (Yeo et al. 2009).

Additional serious viral infections, new, reactivated, or exacerbated (e.g., infections caused by cytomegalovirus, varicella zoster virus, herpes simplex virus, West Nile virus, parvovirus B19, John Cunningham [JC] virus, and HCV) have been reported with rituximab, mainly in patients who had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Particular attention should be given to patients who have had significant prior immunosuppressive treatment

such as high-dose chemotherapy and stem cell transplant. JC virus infection resulting in PML and death has been observed in rituximab-treated patients with hematologic malignancies or with autoimmune diseases. Most cases of progressive multifocal leukoencephalopathy (PML) were diagnosed within 12 months of the patient's last infusion of rituximab. Physicians should consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. Physicians should discontinue rituximab (and DCDT2980S and/or DCDS4501A) and consider discontinuation or reduction of any immunosuppressive therapy in patients who develop PML.

3.4.4.5 Cardiovascular Events

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with preexisting cardiac conditions, including arrhythmias and angina, who have had recurrences of these events during rituximab therapy should be monitored throughout the infusion and the immediate post-infusion period.

3.4.4.6 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, were observed in patients receiving rituximab in combination with chemotherapy for DLBCL. In post-marketing reports, which include patients with low-grade or follicular NHL and patients with DLBCL, the mean time to onset of symptoms was 6 days (range, 1–77 days) in patients with documented gastrointestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

3.4.4.7 Immunization

The safety of immunization with live viral vaccines following rituximab therapy has not been studied. Patients who participate in this study may not receive either primary or booster with live virus vaccines for at least 28 days prior to initiation of rituximab or at any time during study treatment. Investigators should review the status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult with non-live vaccines intended to prevent infectious diseases prior to study therapy.

Refer to the Rituxan®/MabThera® (Rituximab) Package Insert/Summary of Product Characteristics (SmPC) for additional safety information.

3.4.5 Risks Associated with Obinutuzumab Therapy

No evidence available at the time of the approval of this protocol indicates that special warnings or precautions are appropriate other than those noted in the Obinutuzumab Investigator's Brochure and as described in the following sections.

3.4.5.1 Infusion-Related Reactions and Hypersensitivity Reactions (including Anaphylaxis)

The commonly experienced IRRs have been characterized by fever, chills, flushing, nausea, vomiting, hypotension, hypertension, fatigue, and other symptoms.

Respiratory infusion-related symptoms, such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema, have also been reported. These IRRs were mostly mild or moderate (NCI CTCAE v4.0, Grade 1 and 2 events), and $<10\%$ of the events were severe (Grade 3 events), occurring predominantly during the first hour of the infusion or shortly after the first infusion had finished. The events resolved with the slowing or interruption of the infusion and supportive care. The incidence and severity of IRRs decreased with subsequent infusions. Extensive tumor burden predominantly localized in the blood circulation (e.g., high peripheral lymphocyte count in patients with CLL) may be a predisposing factor for the development of IRRs.

IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions.

3.4.5.2 Tumor Lysis Syndrome

TLS has been reported with obinutuzumab administration. Patients with a high tumor burden, including patients with a lymphocyte count $\geq 25 \times 10^9$/L, particularly patients with B-cell CLL and MCL, are at increased risk for TLS and severe IRRs. All patients with peripheral blood lymphocyte counts of $\geq 25 \times 10^9$/L or bulky adenopathy must receive prophylaxis for TLS prior to the initiation of study treatment. This includes appropriate hydration, consisting of fluid intake of approximately 3 L/day, starting 1–2 days prior to the first dose of obinutuzumab, and administration of allopurinol (300 mg/day orally) or a suitable alternative (i.e., rasburicase) treatment, starting at least $12-24$ hours prior to the first infusion of obinutuzumab (Cycle 1, Day 1). All patients should then be carefully monitored during the initial weeks of treatment. Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts $\geq 25 \times 10^9$/L) before the second and subsequent infusions of obinutuzumab should receive continuous TLS prophylaxis with allopurinol or a suitable alternative (i.e., rasburicase) and adequate hydration until the risk is abated, as determined by the investigator. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

3.4.5.3 Neutropenia

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. Use of G-CSF has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G-CSF is allowed for treatment

of neutropenia in this study. Primary prophylaxis with G-CSF is recommended according to the American Society of Clinical Oncology (ASCO), European Organisation for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines, namely for patients who are ≥60 years old and/or with co-morbidities (Lyman et al. 2004).

3.4.5.4 Thrombocytopenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in patients treated with obinutuzumab. It seems that the first cycle is the greatest risk of hemorrhage in patients treated with obinutuzumab. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants), may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician.

3.4.5.5 Infection

On the basis of its anticipated mode of action, resulting in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Infections have been reported in patients receiving obinutuzumab. Therefore, obinutuzumab should not be administered to patients with active severe infections.

A “black-box” warning for obinutuzumab states that reactivation of hepatitis B as well as other serious viral infections (e.g., infections caused by cytomegalovirus, Varicella zoster virus, herpes simplex virus, JC virus, and HCV) that were new, reactivated, or exacerbated have been reported with the B cell–depleting antibody rituximab mainly in patients who had received the drug in combination with chemotherapy or as part of a hematopoietic SCT. The risk of such infections with obinutuzumab is unknown. Particular attention should be given to patients who have previously received significant immunosuppressive treatment, such as high-dose chemotherapy and SCT.

A “black-box” warning for obinutuzumab states that JC viral infection (including fatal) that resulted in PML with destructive infection of oligodendrocytes of the CNS white matte have been reported in patients treated with anti-CD20 therapies, including rituximab and obinutuzumab.

The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract

findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as cortical (e.g., aphasia or visual-spatial disorientation) can occur.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA).

Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the diagnosis and management of PML.

3.4.5.6 Immunization

The safety of immunization with live virus vaccines following obinutuzumab therapy has not been studied. Thus, vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

3.4.5.7 Worsening of Preexisting Cardiac Condition

In patients with underlying cardiac disease and treated with obinutuzumab, adverse events such as angina pectoris, acute coronary syndrome, myocardial infarction, heart failure, and arrhythmias, including atrial fibrillation and tachyarrhythmia, have been observed. These events may occur as part of an IRR and can be fatal. Therefore, patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution to prevent a potential fluid overload.

3.5 MINIMIZATION OF BIAS

For the randomized, non-comparative, open-label portion of the study, patients were randomly allocated to two treatment arms in a 1:1 ratio through use of an interactive voice or web-based response system (IxRS). A dynamic stratified randomization scheme was employed to ensure balance in the stratification factors as specified in Section 3.1. This portion of the study (Arms A and B) is now closed to enrollment.

3.6 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche group, will sponsor this study. A Contract Research Organization (CRO) will be utilized to perform project management, study management, and clinical monitoring. Genentech will conduct CRO oversight, approve patient eligibility, and perform dose escalation decision-making, medical monitoring, and statistical programming and analysis. An IMC (see Section 3.4) will provide an additional level of safety monitoring for the study.

Approximately 40 study centers in the United States, Canada, and Europe will participate in the study to enroll approximately 252 patients. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

Electronic data capture (EDC) will be utilized for this study. An IxRS will be used to assign patient numbers. A central laboratory will be used for sample management and storage until shipment to one of several specialty laboratories or Genentech for analysis. An IRF will be used for the collection and possible assessment of radiographic images from tumor assessments. Additional vendors for ECG collection and possible analysis and for PRO collection and data entry will be used.

3.7 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with the FDA regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws, as well as other applicable country laws.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria to be eligible for study entry:

- Signed Informed

  Consent Form(s)
- Age ≥ 18 years
- ECOG Performance Status of 0, 1, or 2
- Life expectancy of at least 12 weeks
- History of histologically documented relapsed or refractory Grades 1–3a FL or relapsed or refractory DLBCL
- Availability of an archival or freshly biopsied tumor tissue sample must be confirmed for study enrollment.
- Have a clinical indication for treatment as determined by the investigator
- Must have at least one bidimensionally measurable lesion (>1.5 cm in its largest dimension by CT scan or MRI)
- Laboratory values (including patients with hepatic or renal involvement), as follows:

  AST and ALT $\leq 2.5 \times$ ULN

  Total bilirubin $\leq 1.5 \times$ ULN

  Platelet count $\geq 75{,}000/mm^3$ (unless thrombocytopenia clearly due to marrow involvement of NHL and/or disease-related immune thrombocytopenia)

  Absolute neutrophil count $\geq 1000/mm^3$ (without growth factor support, unless neutropenia clearly due to marrow involvement of NHL)

  Total hemoglobin ≥ 9 g/dL (without transfusion support >14 days prior to screening, unless anemia clearly due to marrow involvement of NHL)

  Serum creatinine ≤ 2.0 mg/dL or measured creatinine CL ≥ 50 mL/min

- For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one highly effective form of nonhormonal contraception or two effective forms of nonhormonal contraception, **including at least one method with a failure rate of < 1% per year**, through the course of study treatment and for ≥12 months after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab (whichever is later) in women and at least 5 months after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab (whichever is later) in men

  A woman is considered <u>not</u> to be of childbearing potential if she is postmenopausal, defined by amenorrhea of ≥12 months duration and age ≥45 years, or has undergone hysterectomy and/or bilateral oophorectomy.

  The following are considered highly effective forms of contraception: 1) true abstinence; 2) male sterilization (with post-procedure documentation of absence of sperm in the ejaculate). For female patients, the sterilized male partner should be the sole partner.

  The following are considered effective forms of contraception: 1) intrauterine device (IUD; copper IUD or hormonal IUDs only) or intrauterine system; 2) condom with spermicidal foam/gel/film/cream/suppository; 3) occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.

  Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab (whichever is later).

4.1.2 <u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

- Prior use of any MAb, radioimmunoconjugate or ADC within 4 weeks before Cycle 1, Day 1
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational anti-cancer agent within 2 weeks prior to Cycle 1, Day 1

  Adverse events except for sensory neuropathy from any previous treatments must be resolved or stabilized to Grade ≤2 prior to Cycle 1, Day 1.
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1, Day 1
- Prior allogeneic stem cell transplant
- Eligibility for autologous SCT (patients with relapsed or refractory DLBCL)
- History of transformation of indolent disease to DLBCL
- History of severe allergic or anaphylactic reactions to MAb therapy (or recombinant antibody-related fusion proteins)

- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma (e.g., of the cervix or breast) are allowed. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥ 2 years prior to Cycle 1, Day 1.

- Current or past history of CNS lymphoma
- Current Grade > 1 peripheral neuropathy
- Evidence of significant, uncontrolled, concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Recent major surgery within 6 weeks prior to Cycle 1, Day 1, other than for diagnosis
- Presence of positive test results for hepatitis B (HBsAg and/or total anti-HBc) or hepatitis C (HCV antibody)

  Patients who are positive for anti-HBc are eligible only if PCR is negative for HBV DNA and it is believed by both the investigator and Medical Monitor that it is in the patient's best interest to participate.

  Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.

- Vaccination with a live vaccine within 28 days prior to treatment
- Known history of HIV seropositive status
- Women who are pregnant or lactating
- Ongoing corticosteroid use > 30 mg/day prednisone or equivalent

  Patients receiving corticosteroid treatment ≤ 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor via facsimile and obtain the Sponsor's approval to

enroll the patient. Once the Sponsor reviews and approves the patient for enrollment, the patient number will be assigned via IxRS.

As described in Section 3.1.1.2, only select investigator sites that have agreed to participate in the non-randomized (Cohorts C and D) portion of the study will enroll patients into these cohorts. Cohorts C and D will be opened sequentially following completion of the randomized portion of the study for patients with FL.

For obinutuzumab-containing cohorts (Cohorts E, G, and H), patients with either relapsed or refractory follicular NHL or relapsed or refractory DLBCL will be enrolled. After the safety run-in stage for DCDS4501A at 1.8 mg/kg in combination with obinutuzumab, the non-randomized dose-expansion portion of the study will enroll 40 relapsed or refractory FL patients into Cohort G and 40 relapsed or refractory DLBCL patients into Cohort H.

Personnel responsible for performing PK and ATA assays will receive participants' treatment assignments to identify appropriate PK and ATA samples to be analyzed in the appropriate corresponding assays.

4.3 STUDY TREATMENT

4.3.1 DCDT2980S and DCDS4501A

4.3.1.1 Formulation and Storage

a. DCDT2980S

DCDT2980S will be provided as a lyophilized powder in a single-use 20-cc vial. The solution for reconstitution is Sterile Water for Injection (SWFI), and the reconstitution volume is 2.6 mL to yield a final concentration of 20 mg/mL DCDT2980S in 40 mM L-histidine hydrochloride, 240 mM sucrose, and 0.02% polysorbate 20, pH 6.0.

Reconstituted DCDT2980S should be further diluted with sterile 0.9% NaCl to a total volume of 250 mL.

DCDT2980S vials must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. DCDT2980S should not be used beyond the expiration date provided by the manufacturer. Vial contents should not be frozen or shaken and should be protected from direct sunlight. After reconstitution, DCDT2980S vials may be stored at room temperatures (> 8°C–25°C [> 46°F–77°F]) for up to 4 hours or at refrigerated temperatures (2°C–8°C [36°F–46°F]) for up to 8 hours prior to use. Once DCDT2980S has been diluted with sterile 0.9% NaCl, the solution should be used within 4 hours at room temperature or within 8 hours at refrigerated temperature. Vials are intended for single use only; therefore, any remaining solution should be discarded.

For further details, refer to the DCDT2980S Investigator's Brochure.

b. DCDS4501A

DCDS4501A is provided as a liquid formulation and contains no preservatives. Each single-use 20-cc vial is filled to deliver 100 mg of DCDS4501A. The drug product is formulated as 10 mg/mL DCDS4501A in 20 mM L-histidine acetate, 240 mM sucrose, 0.02% (w/v) polysorbate 20, pH 5.5.

DCDS4501A will be administered to patients intravenously via syringe pump with an IV infusion set containing a 0.22−µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight.

DCDS4501A vials must be refrigerated at 2°C−8°C (36°F−46°F) upon receipt until use. DCDS4501A vials may be stored at room temperature (> 8°C−25°C [46°F−77°F]) for up to 8 hours. DCDS4501A should not be used beyond the expiration date provided by the manufacturer. Vial contents should not be frozen or shaken and should be protected from direct sunlight. Vials are intended for single use only; therefore, any remaining solution should be discarded.

Once the DCDS4501A dose solution has been prepared, the solution should be used within 4 hours at room temperature (> 8 °C−25°C [46°F−77°F]) or within 8 hours refrigerated at 2°C−8°C (36°F−46°F). Because the drug product contains no preservatives, the Sponsor recommends using DCDS4501A in a syringe and extension set as soon as possible to reduce the risk of microbial contamination.

For further details, refer to the DCDS4501A Investigator Brochure.

4.3.1.2 Dosage and Administration

a. DCDT2980S-Specific Information

DCDT2980S will be administered to patients by IV infusion. Compatibility testing has shown that DCDT2980S is stable when diluted in polyvinyl chloride (PVC) bags to a concentration at or above 0.04 mg/mL in 0.9% NaCl diluent. The drug product will be delivered following dilution in 0.9% NaCl with a final DCDT2980S concentration determined based on dose and patient weight. The study drug will be diluted in a PVC bag and delivered using a 0.22 µm in-line filter on the IV infusion set.

Additional information/instructions regarding study drug administration will be provided in the Pharmacy Binder.

b. DCDS4501A-Specific Information

DCDS4501A will be administered to patients intravenously via syringe pump with an IV infusion set containing a 0.22 µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight. Compatibility testing has shown that DCDS4501A is stable both in syringes made of polypropylene (PP) and in standard extension sets with 0.22 µm in-line filter, when stored neat or diluted with 0.9% NaCl saline.

Additional information/instructions regarding study drug administration will be provided in the Pharmacy Binder.

c. General Information

The total dose of DCDT2980S and DCDS4501A for each patient will depend on the patient's weight within 96 hours prior to Day 1 of each cycle. The patient weight obtained during screening may be used for dose determination at all treatment cycles; if the patient's weight within 96 hours prior to Day 1 of a given treatment cycle differs by >10% from the weight obtained during screening, the new weight should be used to calculate the dose.

For both DCDT2980S and DCDS4501A, the initial dose will be administered to well-hydrated (based on clinical judgment) patients over 90 (±10) minutes. Premedication with acetaminophen or paracetamol (e.g., 500–1000 mg) and diphenhydramine (e.g., 50°C–100 mg) per institutional standard practice may be administered prior to each infusion. Administration of corticosteroids is permitted at the discretion of the treating physician. Patients who do not receive premedications prior to the first dose of DCDT2980S and who develop an IRR during the first dose should receive premedications prior to subsequent doses (see Table 1).

The DCDT2980S/DCDS4501A infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. Following the initial dose, patients will be observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If the infusion is well-tolerated, subsequent doses of DCDT2980S/DCDS4501A may be administered over 30 (±10) minutes, followed by a 30-minute observation period post-infusion.

For instructions on study drug preparation and administration, refer to the DCDT2980S and DCDS4501A Investigator Brochure.

4.3.1.3 Dosage Modification

Patients should be assessed clinically for toxicity prior to each dose using the NCI CTCAE v4.0 grading scale. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable. If scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date, with subsequent dosing continuing on a 21-day schedule as applicable.

Specific guidelines around dosage modifications for neutropenia and peripheral neuropathy are detailed below in Section 4.3.1.6 and Section 4.3.1.7. Patients who experience other treatment-related Grade 3 or 4 toxicity or laboratory abnormalities will be allowed to delay dosing of study treatment (both ADC and rituximab or obinutuzumab) for up to 2 weeks to allow for recovery. Patients may continue to receive additional infusions of DCDT2980S or DCDS4501A per their treatment assignment provided that the toxicity has resolved to Grade ≤2 or ≥80% of the baseline value,

whichever is lower, within the 2–week delay period. The decision for dose modification will be made on the basis of the investigator's assessment of ongoing clinical benefit with continued study treatment and in consultation with the Medical Monitor.

Once dose reductions of DCDT2980S or DCDS4501A are made for toxicity, dose re-escalation will not be allowed.

If a patient develops unacceptable toxicity to DCDT2980S or DCDS4501A, requiring its discontinuation, single-agent rituximab may be continued on the basis of the investigator's assessment of ongoing clinical benefit and with the approval of the Medical Monitor. Patients enrolled in obinutuzumab-containing cohorts will not continue on single-agent obinutuzumab unless approved by the Medical Monitor.

4.3.1.4 Schedule Modification

Patients in whom toxicities have not resolved to Grade ≤ 2 or $\geq 80\%$ of baseline value, whichever is lower, may have their study treatment delayed by up to 2 weeks. Dosing of both DCDT2980S or DCDS4501A and rituximab or obinutuzumab should be held during this period. If all study drug–related toxicities have resolved sufficiently, the patient may resume DCDT2980S or DCDS4501A and rituximab or obinutuzumab dosing on the regular every-21-day schedule.

A patient's dosing may be changed to a 28-day cycle if it is felt by the investigator that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from a transient and reversible toxicity—for example, cytopenia without requiring repeated treatment delays. Modifications to the dosing schedule in this fashion must be made in consultation with and with the approval of the Medical Monitor.

Patients who do not fulfill the criteria for continuation of dosing after the 2-week delay may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.6). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

Specific guidelines around schedule modifications for neutropenia and peripheral neuropathy are detailed below in Section 4.3.1.6 and Section 4.3.1.7.

4.3.1.5 Infusion Reaction

Patients will be monitored during and after each DCDT2980S/DCDS4501A infusion for 90 minutes after the first infusion and for 30 minutes after subsequent infusions in the absence of infusion-related adverse events. Patients who experience infusion-related symptoms should be managed as described in Table 1. Precautions for suspected anaphylactic reaction during study drug infusions are provided in Appendix D.

In the event of a life-threatening IRR, which may include pulmonary or cardiac events, or an IgE-mediated anaphylactic reaction, administration of DCDT2980S/DCDS4501A should be immediately discontinued. Patients who experience these reactions should receive aggressive symptomatic treatment and are not eligible to receive any additional study treatment.

Premedication prior to DCDT2980S/DCDS4501A with acetaminophen/paracetamol, antihistamines, or corticosteroids per standard clinical practice is permitted—for example, in patients with substantial tumor burden and where the risk of cytokine release syndrome is high. In patients who do not receive premedication prior to any given dose of DCDT2980S/DCDS4501A and who develop any Grade ≥ 2 infusion-related toxicity, premedication should be administered prior to subsequent doses.

Table 1 Management of Infusion-Related Symptoms for All Study Drugs

Infusion-Related Symptoms [a]	Guidance
Grade 1–2	• Slow or hold infusion • Give supportive treatment [b] • Upon symptom resolution, may resume/escalate infusion rate at the investigator's discretion [c] • Note: For Grade 2 wheezing or bronchospasm, patient must be premedicated for subsequent doses. If symptoms recur with the same or greater severity, the infusion must be stopped immediately and study treatment permanently discontinued.
Grade 3	• Discontinue infusion • Give supportive treatment [b] • Upon symptom resolution, may resume/escalate infusion rate at the investigator discretion [c] • Note: If the same adverse event recurs with the same or greater severity, treatment must be permanently discontinued. • Note: For Grade 3 hypotension or fever, patient must be premedicated before re-treatment. If symptoms recur, then study drug must be permanently discontinued. • Note: If patient has Grade 3 wheezing or bronchospasm at first occurrence, study treatment should be permanently discontinued.
Grade 4	• Discontinue infusion immediately, treat symptoms aggressively, and permanently discontinue patient from study treatment

IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Refer to the NCI CTCAE v4.0 scale for the grading of symptoms. Management of IgE-mediated allergic reactions should be as directed in the text preceding this table.

[b] Supportive treatment: Patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the last 4 hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators. Patients with hypotension requiring vasopressor support must be permanently discontinued from study drug.

[c] Infusion rate escalation after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hr every 30 minutes.

4.3.1.6 Neutropenia

Because neutropenia is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.3.3), the use of growth factor support (G-CSF) as prophylactic and therapeutic indications is permitted (see Appendix F) in order to allow continued dosing of DCDT2980S/DCDS4501A. Dose modifications for patients who experience treatment-related Grade 3–4 neutropenia in the context of G-CSF usage are as follows:

- Primary prophylaxis with G-CSF (i.e., prior to the first dose of DCDT2980S/DCDS4501A) is permitted for patients with clinical factors listed in Appendix F or who otherwise are considered at high risk for developing neutropenia on study treatment.
- Patients who experience treatment-related Grade 3–4 neutropenia will be allowed to delay dosing of study treatment (both ADC and rituximab or obinutuzumab) for up to two weeks to allow for recovery. Therapeutic G-CSF is permitted as clinically indicated (see Appendix F) and to facilitate neutrophil recovery to allow subsequent DCDT2980S/DCDS4501A dosing.
- Subsequent dosing of DCDT2980S/DCDS4501A and rituximab/obinutuzumab is permitted provided that the neutropenia has resolved to Grade ≤ 2 or $\geq 80\%$ of the baseline value, whichever is lower, within the 2-week period.
- If prophylactic G-CSF was not administered prior to the cycle in which the Grade 3–4 neutropenia developed, then prophylactic G-CSF may be administered prior to subsequent cycles without DCDT2980S/DCDS4501A dose reduction. The dose schedule may be changed from 21-day to 28-day cycles to provide sufficient time for neutrophil recovery in subsequent cycles. In the absence of prophylactic G-CSF or dose schedule modification, the dose of DCDT2980S/DCDS4501A in subsequent cycles should be reduced to 1.8 mg/kg for Arms A and B. For Cohorts E, G, and H, patients will be given DCDS4501A at a dose of 1.8 mg/kg, and further dose reductions cannot be made.
- If Grade 3–4 neutropenia recurs with prophylactic G-CSF, the dose for subsequent DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg for Arms A and B. Prophylactic G-CSF and dose schedule modifications as described above are permitted in order to maintain the reduced DCDT2980S/DCDS4501A dose level and schedule.
- If Grade 3–4 neutropenia recurs at the reduced dose despite the administration of prophylactic G-CSF, then the patient should be discontinued from study treatment.
- For patients enrolled into the non-randomized portion of the study (Cohorts C and D, as well as Cohorts E, G, and H), dose reductions will not be allowed for neutropenia. Administration of therapeutic/prophylactic G-CSF and dose-schedule modifications as described above are allowed. Patients who have persistent or recurrent Grade 3–4 neutropenia as defined above should be discontinued from study treatment.

The determination of the dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment and with the approval of the Medical Monitor.

4.3.1.7 Peripheral Neuropathy

Peripheral neuropathy (sensory and/or motor) is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.3.5). For new or worsening drug-related Grade 2 or 3 peripheral sensory and/or motor neuropathy, dosing should be held for up to 2 weeks until peripheral neuropathy improves to Grade 1 or baseline grade. Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and approval of the Medical Monitor based on an assessment of the benefit-risk analysis of continuing to delay study treatment.

For patients enrolled in arms A or B following resolution of peripheral neuropathy (sensory and/or motor), subsequent doses of DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg. If worsening Grade 2 or 3 peripheral neuropathy (sensory and/or motor) recurs following dose reduction, study treatment should be discontinued. For Grade 4 peripheral neuropathy (sensory and/or motor), study treatment should be discontinued.

For patients enrolled into Cohorts C and D, dose modifications will not be allowed. Patients who have Grade 2 or 3 peripheral neuropathy (sensory and/or motor), as defined above, should be discontinued from study treatment.

For patients enrolled in Cohorts E, G, or H, following resolution of Grade 2 or Grade 3 peripheral neuropathy (sensory and/or motor), subsequent doses of DCDS4501A should be permanently reduced from 1.8 mg/kg to 1.4 mg/kg. If worsening Grade 2 or Grade 3 peripheral neuropathy (sensory and/or motor) recurs following dose reduction, study treatment should be discontinued. For Grade 4 peripheral neuropathy (sensory and/or motor), study treatment should be discontinued.

4.3.1.8 Hyperglycemia

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other ADCs using the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation of improved anti-hyperglycemic medications (see Section 3.4.3.7).

For symptomatic fasting Grade 3 ($>$250–500 mg/dL) or asymptomatic Grade 4 ($>$500 mg/dL) hyperglycemia, medical management should be initiated immediately and consultation with a specialist should be considered. If the hyperglycemia persists for $>$1 week after initiation of management, dose modification, schedule modification, or discontinuation of study treatment should be considered. In these cases, the study Medical Monitor should be consulted to assess the benefit-risk balance of continued study treatment.

4.3.2 Rituximab

4.3.2.1 Formulation

Rituximab (Rituxan®/MabThera®) is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in 500-mg (50-mL) single-use vials. A single-unit, 500-mg carton contains one 50-mL vial of rituximab (10 mg/mL). The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, and 0.7 mg/mL polysorbate 80, after reconstitution with SWFI. The pH is adjusted to 6.5. Vials are for single use. Each vial and carton will contain a label (either single-panel or booklet) affixed to the vial or carton.

4.3.2.2 Dosage, Administration, and Storage

Rituximab (Rituxan®, MabThera®) will be administered intravenously once per 3-week (or 4-week) cycle. The infusion at 375 mg/m^2 for each dose will be based on the patient's body surface area at screening and will remain the same throughout the study.

If a scheduled dose of rituximab falls outside of the ±2-day window for reasons other than an adverse event, the site must notify and have a discussion with the Genentech Medical Monitor prior to rituximab administration. Such dosing may not necessarily qualify as a protocol deviation, if deemed to be in the best interests of the patient, after consultation with the Medical Monitor and agreed to in advance by the Medical Monitor.

Rituximab should not be administered as an IV push or bolus. Infusion reactions may occur. Premedication consisting of acetaminophen (or paracetamol), diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (e.g., up to 100 mg or an equivalent dose of methylprednisolone) may also be administered beginning with the first infusion, per standard clinical practice. Premedication may attenuate infusion reactions. Because transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

a. First Infusion

The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If infusion reactions do not occur, the infusion rate should be escalated in 50–mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

b. Subsequent Infusions

If the patient tolerates the first infusion well, subsequent rituximab infusions may be administered at an initial rate of 100 mg/hr and increased in 100–mg/hr increments at 30-minute intervals to a maximum of 400 mg/hr, as tolerated. If the patient does not tolerate the first infusion well, the guidelines for the first infusion should be followed.

If a patient tolerates the first three cycles of study treatment without significant infusion reactions, rituximab may be administered as “rapid infusion” in accordance with local institutional guidelines.

c. Storage

Rituximab vials must be stored at 2°C–8°C (36°C–46°F). Rituximab vials should be stored in the outer carton in order to protect them from light. Rituximab solution for infusion may be stored at 2°C–8°C (36°C–46°F) for 24 hours and has been shown to be stable for an additional 12 hours at room temperature. However, because rituximab does not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between rituximab and PVC or polyethylene (PE) bags have been observed.

See the Rituxan® (Rituximab) Package Insert or SmPC (in the European Union) for additional information.

4.3.2.3 Dosage Modification

There will be no rituximab dose modification in this study. Patients at high risk for TLS complications (see Section 3.4.3.2) may, at the investigator’s discretion, receive their initial dose of rituximab over 2 consecutive days (e.g., 125 mg/m^2 on Day 1, 250 mg/m^2 on Day 2; with DCDT2980S/DCDS4501A dose potentially delayed to Day 3).

Any NCI CTCAE (v4.0) toxicity Grade ≥ 3 in severity that is deemed related to rituximab treatment will require interruption of study treatment (both ADC and rituximab) until resolution to Grade ≤ 2 or ≥ 80% of baseline, whichever is lower. Resumption of rituximab treatment may be considered in patients with resolution of toxicities to Grade ≤ 1 within 2 weeks at the discretion of the investigator, after consultation with the Medical Monitor. Failure of such toxicities to resolve after 2-week delay in study treatment will require permanent discontinuation of rituximab. Continuation of rituximab treatment may be permitted on the basis of ongoing clinical benefit following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

If a patient develops unacceptable toxicity to rituximab requiring its discontinuation, single-agent DCDT2980S or DCDS4501A may be continued on the basis of the investigator’s assessment of ongoing clinical benefit and with the approval of the Medical Monitor.

4.3.2.4 Schedule Modification

Patients in whom toxicities have not resolved (i.e., to Grade ≤ 1 or ≥ 80% of baseline) may have their study treatment delayed by up to 2 weeks. If after the up to–2-week delay, all study drug–related toxicities have resolved sufficiently, the patient may receive the scheduled doses of rituximab. In addition, a patient’s dosing may be changed to a 28-day cycle if it is felt by the investigator and Medical Monitor that changing a patient’s

dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from transient cytopenias without requiring repeated treatment delays.

Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.1). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

4.3.2.5 Infusion Reaction

Patients will be monitored during and after each rituximab infusion for 90 minutes after the first infusion and for 30 minutes after subsequent infusions in the absence of infusion-related adverse events. Patients who experience infusion-related symptoms should be managed as directed in Table 1 (see Section 4.3.1.5).

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction to rituximab, rituximab should be discontinued and no additional rituximab should be administered. Patients who experience these reactions should receive aggressive symptomatic treatment and should be discontinued from study treatment.

4.3.3 Obinutuzumab

4.3.3.1 Formulation

Obinutuzumab (GA101/Gazyva™/Gazyvaro) is a clear, colorless to slightly brownish liquid, provided as a single 1000-mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50–mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188, and highly purified water (HPW).

4.3.3.2 Dosage, Administration, and Storage

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg in combination with DCDS4501A, as outlined in Section 3.1.3. Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–8 (see Table 2). No dose modifications of obinutuzumab are allowed.

All obinutuzumab infusions should be administered after premedication with oral acetaminophen and an antihistamine (see Section 4.4.1). The prophylactic use of corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) may also be considered for patients thought to be at high risk for IRRs, if deemed appropriate by the investigator, and should be administered prior to the obinutuzumab infusion. On Cycle 1 Day 1, it is recommended that oral prednisone, prednisolone, or methylprednisolone be given within 12 hours as a premedication but at least 60 minutes prior to the obinutuzumab infusion.

Premedication with prednisone or prednisolone is mandatory in patients who had an IRR and should continue until IRRs no longer occur during antibody infusion. For the management of IRRs and anaphylaxis, see Table 1 (Section 4.3.1.5).

If it is the strong preference of the investigator or of the site (e.g., for logistical reasons) or if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count), the administration of obinutuzumab infusion can be split over 2 days.

Table 2 Administration of First and Subsequent Infusions of Obinutuzumab

First Infusion (Cycle 1 Day 1)	Subsequent Infusions
• Begin infusion at an initial rate of 50 mg/hr. • If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/hour increments every 30 minutes to a maximum of 400 mg/hr. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate used at the time the reaction occurred).	• If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, use full premedication including 100 mg prednisone/prednisolone (until no further IRR occurs), begin infusion at an initial rate of 50 mg/hr, and follow instructions for first infusion. • If the patient tolerated the prior infusion well (defined by absence of Grade 2 reactions during a final infusion rate of ≥100 mg/hr), begin infusion at a rate of 100 mg/hr. • If no reaction occurs, increase the infusion rate in 100-mg/hour increments every 30 minutes, to a maximum of 400 mg/hr. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate used at the time the reaction occurred).

IRR = infusion-related reaction.

In all parts of the study, obinutuzumab must be administered in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available, and patients should be under the close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Table 1 (Section 4.3.1.5).

Obinutuzumab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. Administration sets with PVC, polyurethane (PUR), or PE as a product contact surface and IV bags with polyolefin (PO), polypropylene (PP), PVC, or PE as a product contact surface are compatible and can be used. Do not use an additional in-line filter because of potential adsorption.

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For clinical formulation-specific and batch-specific instructions and information on in-use stability, see the packaging label.

4.3.3.3 Dosage Modification

There will be no obinutuzumab dose modification in this study. Patients at high risk for TLS complications (see Section 3.4.3.2) may, at the investigator's discretion, receive obinutuzumab over 2 consecutive days (with DCDS4501A dose potentially delayed to Day 2 or Day 3).

Any NCI CTCAE (v4.0) toxicity Grade ≥3 in severity that is deemed related to obinutuzumab treatment will require interruption of study treatment (both DCDS4501A and obinutuzumab) until resolution to Grade ≤2 or ≥80% of baseline, whichever is lower. Resumption of obinutuzumab treatment may be considered in patients with resolution of toxicities to Grade ≤1 within 2 weeks at the discretion of the investigator, after consultation with the Medical Monitor. Failure of such toxicities to resolve after 2-week delay in study treatment will require permanent discontinuation of obinutuzumab. Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and approval of the Medical Monitor based on an assessment of the benefit-risk analysis of continuing to delay study treatment.

If a patient develops unacceptable toxicity to obinutuzumab requiring its discontinuation, single-agent DCDS4501A will not be permitted.

4.3.3.4 Schedule Modification

Patients in whom toxicities have not resolved (i.e., to Grade ≤1 or ≥80% of baseline) may have their study treatment delayed by up to 2 weeks. Dosing of both DCDS4501A and obinutuzumab should be held during this period. If all study drug–related toxicities have resolved to Grade ≤*1* or ≥ 80% of baseline, the patient may resume DCDS4501A and obinutuzumab dosing on the regular every–21–day schedule. In addition, a patient's dosing may be changed to a 28-day cycle if it is felt by the investigator and Medical Monitor that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from transient cytopenias without requiring repeated treatment delays.

Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.6). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

Specific guidelines around schedule modifications for thrombocytopenia and febrile neutropenia are detailed below in Section 4.3.3.5 and Section 4.3.3.6.

4.3.3.5 Thrombocytopenia

Thrombocytopenia is a known risk of obinutuzumab (see Section 3.4.5.4). If the clinical condition of a patient requires the use of concomitant anticoagulants, the patient is at increased risk of bleeding when the platelet count is $<$20,000/μL. When possible, replace prior therapy with Vitamin K antagonists, such as warfarin, with low-molecular weight heparin (LMWH) or new oral anticoagulants (NOACs) before Cycle 1 Day 1. Clinical decision making may be adjusted depending on the patient-specific assessment of benefit and risk.

In the event of severe thrombocytopenia (platelet count $<$10,000/μL) and/or symptomatic bleeding (irrespective of platelet count) in patients who are not receiving concomitant anticoagulants or platelet inhibitors:

- Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves. If Cycle 1 Day 8 is delayed, then skip Day 8 and administer Day 15 as previously scheduled (if thrombocytopenia or symptomatic bleeding has resolved). If Cycle 1 Day 15 is delayed, then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab and DCDS4501A as scheduled (if thrombocytopenia or symptomatic bleeding has resolved).

In the event of thrombocytopenia with platelet count $<$20,000/μL and/or symptomatic bleeding (irrespective of platelet count) in patients who are receiving concomitant anticoagulants or platelet inhibitors:

- Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves. If Cycle 1 Day 8 is delayed, then skip Day 8 and administer Day 15 as previously scheduled (if thrombocytopenia or symptomatic bleeding has resolved). If Cycle 1 Day 15 is delayed, then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab and DCDS4501A as scheduled (if thrombocytopenia or symptomatic bleeding has resolved).
- For patients who are on LMWH or NOACs, when platelet count $<$20,000/μL develops, reduce the dose of LMWH or NOACs used.
- For patients who are on platelet inhibitors when thrombocytopenia with platelet count $<$20,000/μL develops, consideration should be given to temporarily pausing the use of platelet inhibitors.

4.3.3.6 Febrile Neutropenia

In the event of febrile neutropenia or neutropenia with infection, hold obinutuzumab until febrile neutropenia or neutropenia with infection resolves.

- If Cycle 1 Day 8 is delayed long enough that the patient is approaching Day 15, then skip Day 8 and administer Day 15 as previously scheduled (if infection or fever has resolved)

- If Cycle 1 Day 15 is delayed long enough that the patient approaching Cycle 2, then skip Day 15 dosing and administer Cycle 2 Day 1 of DCDS4501 as scheduled (if infection or fever has resolved)
- Note: Obinutuzumab Patients will receive DCDT2980S or DCDS4501A at 1.8 mg/kg or 2.4 mg/kg by IV infusion on Day 1 or Day should not be held for neutropenia without fever or infection

4.3.4 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (pinatuzumab vedotin [DCDT2980S], polatuzumab vedotin [DCDS4501A], rituximab, and obinutuzumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will be either disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Concomitant Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by a patient from 7 days prior to the screening evaluation to the end of study visits. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF). Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Concomitant use of hematopoietic growth factors is allowed in accordance with instructions provided in the package inserts.

Patients who experience infusion-related temperature elevations of $>38.5°C$ ($>101.3°F$) or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol ($\geq$ 500 mg) and/or H1 and H2 histamine-receptor antagonists (e.g., diphenhydramine, ranitidine). Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with additional supportive therapies (e.g., supplemental oxygen, β2-agonists, and/or corticosteroids) as clinically indicated according to standard clinical practice (see Table 1).

For patients enrolled in obinutuzumab-containing regimens, it is recommended that corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) be given as premedication within 12 hours of, but at least 60 minutes prior to, the obinutuzumab infusion on Cycle 1 Day 1. After the first obinutuzumab infusion, additional glucocorticoids are allowed at the investigator's discretion. For patients who did not experience infusion-related symptoms with their previous infusion, premedication at subsequent infusions may be omitted at the investigator's discretion.

Infusion reaction prophylaxis with medications (e.g., acetaminophen/paracetamol, antihistamines, and/or corticosteroids) may be instituted at any point in the study if it is determined to be in the best interest of the patient on the basis of the observation of IRRs in patients already enrolled in the study. Patients with Grade 3 hypotension or fever must be premedicated prior to retreatment (see Section 4.3.1.5). Patients with hypotension requiring vasopressor support or with Grade 3 wheezing, hypoxia, or generalized urticaria must be permanently discontinued from study treatment.

4.4.2 Excluded Therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy
- Immunotherapy including immunosuppressive therapy
- Radioimmunotherapy
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Biologic agents (other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts); guidelines for the use of G-CSF are detailed in Section 4.3.1.6 and Appendix F.
- Any therapies intended for the treatment of lymphoma or leukemia, whether approved by local regulatory authorities or investigational

Patients who require the use of any of these agents will be discontinued from all study treatment. Patients who are discontinued from study treatment will be followed for safety outcomes for 30 days following the patient's last dose of DCDT2980S or DCDS4501A or rituximab or obinutuzumab, whichever is later, or until the patient receives another anti-cancer therapy, whichever occurs first.

4.5 STUDY ASSESSMENTS

4.5.1 Definitions of Study Assessments

4.5.1.1 Medical History and Demographics

Medical history includes all clinically significant diseases, prior cancer history, prior cancer therapies and procedures, and all medications used by the patient within 7 days preceding the screening visit.

4.5.1.2 Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure while the patient is in a sitting or semi-supine position, pulse oximetry, pulse rate, and body temperature. Every effort will be made to ensure that vital signs are obtained from patients in a consistent manner and position. The timing of vital sign collection on the days of study treatment administration is as follows:

- For the administration of rituximab or obinutuzumab, vital signs should be assessed prior to the start of the infusion, every 15 (±5) minutes during the first hour of the infusion, as clinically indicated during the remainder of the infusion, and following the completion of the infusion.
- For the administration of DCDT2980S or DCDS4501A, vital signs should be assessed prior to the start of the infusion, every 15 (±5) minutes during the infusion, at the end of the infusion, and every 30 (±10) minutes for 90 minutes post-infusion following dosing at Cycle 1 and 30 (±10) minutes following dosing in subsequent cycles.

Additional monitoring of vital signs should be performed if clinically indicated.

4.5.1.3 Physical Examination

A complete physical examination should include the evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Targeted physical examinations should be limited to systems of clinical relevance (i.e., cardiovascular, respiratory, and any system that might be associated with tumor assessment, such as lymph nodes, liver, and spleen) and those systems associated with symptoms.

Changes from baseline should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

Resolution or any change in grade of peripheral neuropathy AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV). This also applies to AEs for which study drug was discontinued or for patients in the follow-up phase after last dose of study treatment with either ongoing AEs or new onset of an AE. For the AEs referring to the follow-up phase newly initiated, relevant treatments need to be documented with treatment dates.

4.5.1.4 Laboratory Assessments

On days of study drug administration, pre-infusion laboratory samples should be drawn within 4 hours prior to the start of infusion, unless otherwise specified. Local laboratory assessments may be obtained up to 72 hours prior to the start of study treatment administration (see below and Section 4.5.3). Instruction manuals and supply kits will be provided for all central laboratory assessments.

Central Laboratory Assessments

Samples for flow cytometry, PK, bone marrow, and anti-DCDT2980S, anti-DCDS4501A, or anti-obinutuzumab antibody assessments will be sent to one or several laboratories or to Genentech for analyses (see Section 3.6). The following assessments will be conducted:

- Leukocyte immunophenotyping/flow cytometry (fluorescence-activated cell sorting [FACS] lymphocyte subsets)

  Whole-blood samples will be collected to analyze B-cell subsets ($CD19^+$), T-cell counts ($CD3^+$, $CD4^+$, $CD8^+$), and NK cell counts ($CD16^+$, $CD56^+$), by flow cytometry.

- ATA assays

  ATAs to DCDT2980S, DCDS4501A, or obinutuzumab will be determined using validated ELISAs (see Section 4.9).

- PK and PD assays (see Section 4.5.1.6)
- A plasma sample and blood samples will be collected from patients for exploratory research as indicated in Section 4.5.1.9.
- For patients who sign the optional consent, a blood sample will be collected prior to the first dose of study treatment for exploratory research.
- Tumor tissue sample (archival or fresh) will be collected from patients for central pathologic review as described in Section 4.1.1 and Section 4.5.1.9.

Local Laboratory Assessments

Samples for hematology, serum chemistry, liver function, and pregnancy will be analyzed at the study site's local laboratory. Local laboratory assessments may be obtained up to 72 hours prior to start of study treatment administration on Day 1 of the treatment cycle.

- Hematology: includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells)
- Coagulation: aPTT, PT, and INR
- Quantitative immunoglobulins (IgA, IgG, and IgM)

- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid, amylase, and lipase
- Serum γ-glutamyl transpeptidase (GGT) levels will be required at screening only
- Hemoglobin A1c
- Viral serology and detection (screening assessment only and if clinically indicated)

  Hepatitis B (HBsAg and HBcAb; also HBV DNA by PCR if the patient is HBcAb positive)

  HCV antibody
- Pregnancy test

  For women of childbearing potential (see Section 4.1.2), a serum pregnancy test must be performed within 14 days prior to Cycle 1 Day 1.

  Urine pregnancy tests will be performed during the study treatment period. If any urine test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Any patient with a positive serum test will not be allowed to receive any study treatment.

4.5.1.5 Electrocardiogram Assessments

Twelve-lead digital ECG measurements will be obtained in triplicate, with immediately consecutive ECGs obtained until three evaluable ECGs are recorded, at the following timepoints:

- Screening
- 30–60 minutes before the start of DCDT2980S or DCDS4501A infusion in Cycle 1
- 30–60 minutes after the completion of DCDT2980S or DCDS4501A infusion in Cycle 1
- 30–60 minutes after the completion of DCDT2980S or DCDS4501A infusion in Cycle 3
- Day 8 (±1 day) of Cycle 3 time matched (i.e., obtained at the same time of day) with post-DCDT2980s/DCDS4501A infusion ECGs for Cycle 3
- Treatment completion/early termination visit

Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of or suspicion for clinically significant signs or symptoms of cardiac dysfunction.

All ECGs as described above will be submitted to a Sponsor-designated ECG central laboratory for storage and potential analysis. Detailed instructions on ECG acquisitions and transmissions to the ECG central laboratory will be provided in the ECG manual provided for this study.

Representative ECGs at each timepoint should be reviewed by the investigator or a qualified designee. Post-screening ECG measurements should be obtained as close as possible to scheduled serum and plasma PK samples (see Appendices B-1 and B-2) and should be no more than 30 minutes apart. If QTc prolongation (>500 ms and >60 ms longer than the pre-dose baseline value) is noted, ECGs should be repeated until the prolongation is reversed or stabilized. If a PK sample is not scheduled at the timepoint where QTc prolongation is first observed, then an unscheduled sample should be obtained. An evaluation for potential causes of QT prolongation—for example, electrolyte imbalances or concomitant medications—should be performed, study treatment dosing held, and the Medical Monitor notified. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician.

4.5.1.6 Pharmacokinetic and Pharmacodynamic Assessments

Pharmacokinetics of DCDT2980S and DCDS4501A will be characterized by measuring total antibody (conjugated and unconjugated antibody), acMMAE, and free MMAE concentrations using validated methods (see Section 4.9). Plasma samples may also be analyzed for other potential MMAE-containing catabolites, per sponsor's discretion. Pharmacokinetics of rituximab will be characterized by measuring rituximab concentrations using a validated method (see Section 4.9). Pharmacokinetics of obinutuzumab will be characterized by measuring obinutuzumab concentrations with use of a validated method (see Section 4.9). These assessments will allow for further characterization of pharmacokinetics of DCDT2980S and DCDS4501A, the assessment of the drug interaction potential when they are given in combination with rituximab or obinutuzumab, and the investigation of potential correlations between PK parameters and safety and/or activity if data allow and at the sponsor's discretion. Pharmacodynamics of obinutuzumab and DCS4501A may be assessed by monitoring the release of tumor associated DNA following treatment.

4.5.1.7 Immunogenicity Assessments

The immunogenicity evaluation will utilize a risk-based strategy and tiered approach (Rosenberg and Worobec 2004a, 2004b, 2005; Koren et al. 2008) designed to detect and characterize all ATA responses to DCDT2980S and DCDS4501A. Patient samples will first be screened to detect all antibody responses toward DCDT2980S or DCDS4501A. Samples that screen positive will be analyzed in a confirmatory assay (competitive binding with DCDT2980S or DCDS4501A) to assess the specificity of the positive response. Titers will be determined for confirmed positive samples. Further characterization will be assessed by competitive binding with the MAb component of DCDT2980S or DCDS4501A to characterize whether the ATA responses are primarily to the mAb or the linker-drug regions of the ADC. Positive ATA samples will be stored for further characterization of ATA responses, if necessary.

The schedule of sample collection for ATA assessment is outlined in Appendices B-1, B-2, or B-3, depending on the schedule of study treatment administration. Samples for ATA will not be collected during the crossover treatment period.

ATA responses to obinutuzumab will be detected and confirmed using a similar tiered approach. Patient samples will first be screened to detect all antibody responses to obinutuzumab. Samples that screen positive will be analyzed in a confirmatory assay (competitive binding with obinutuzumab) to assess the specificity of the positive response. The relative levels of ATA in confirmed positive samples will be determined in a titering assay. Positive ATA samples will be stored for further characterization of ATA responses, if necessary.

4.5.1.8 Tumor Response Assessments

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, on the basis of physical examinations, CT scans, PET/CT scans, and/or MRI scans, and bone marrow examinations, using standard response criteria for NHL (Cheson et al. 2007; Cheson et al. 2014) (see Appendix C-1 and C-2). *Specific response assessment criteria differ between the rituximab-containing arms/cohorts and the obinutuzumab-containing cohorts (see Section 4.5.1.8a. and 4.5.1.8b).*

a. Radiographic Assessments for Patients on Rituximab-Containing Arms/Cohorts

CT scans with contrast should include chest, abdomen, and pelvis scans; CT scans of the neck should be performed at screening and followed only if disease is present at screening. Post-screening radiographic assessments may be limited to areas of prior involvement only if required by local health authorities.

MRI scans may be used instead of CT scans in patients for whom CT scans with IV contrast are contraindicated. Details regarding imaging procedures in these cases will be provided in the Imaging Manual.

A PET/CT scan is required during screening for all patients with DLBCL. An additional PET/CT scan in patients with DLBCL should be obtained at the 6-month tumor assessment to ensure consistency of response assessment methodology at this timepoint for all patients. PET/CT scans should additionally be obtained to confirm disappearance of metabolically active disease during study treatment and to confirm a CR upon discontinuation of study treatment.

For patients with FL, PET/CT scans are not required but may be obtained on the basis of physician preference and if permitted by local health authorities. Similarly, for patients with DLBCL, PET/CT scans on patients with FL should be obtained during screening; for patients whose tumors are PET positive during screening, an additional PET/CT scan should be obtained at the 6-month tumor assessment. PET/CT scans should

additionally be obtained to confirm disappearance of metabolically active disease during study treatment and to confirm a CR upon discontinuation of study treatment.

For all patients regardless of disease subtype, combined PET/CT scans may be used instead of CT alone if performed with contrast and if collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent PET/CT scans. If a PET/CT scan is to be used during screening, then PET/CT scans should be performed for all subsequent tumor assessments in order to ensure their consistency across different timepoints.

All tumor assessments will be submitted to an IRF for storage and possible independent centralized review. Details related to submission of data to the IRF will be defined in a separate Imaging Manual.

b. Radiographic Assessments for Patients on Obinutuzumab-Containing Cohorts

PET/CT scans should minimally extend from skull-base to mid-thigh. Full-body PET scan should be performed when clinically appropriate.

CT scans with oral and IV contrast should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated. CT scans for response assessment may be limited to areas of prior involvement only if required by local health authorities. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

In patients for whom contrast is contraindicated—for example, patients with contrast allergy or impaired renal CL—CT or combined PET/CT scans without contrast are permitted so long as they permit consistent and precise measurement of target lesions during the study treatment period.

PET/CT scans are required for $patients\ with$ follicular NHL and DLBCL at screening, after Cycle 4 of study treatment (i.e., between Cycle 4 Day 15 and Cycle 5 Day 1), and at EOT. The EOT response assessment should be performed 6–8 weeks after Cycle 8 Day 1 or last study treatment. CT scans without PET scans will be obtained every 6 months for 2 years, with use of Lugano 2014 Response Criteria for NHL (see Appendix C-2).

c. Bone Marrow Assessments

A bone marrow biopsy for morphology is required at screening and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. For obinutuzumab-containing cohorts, only follicular NHL patients are required to undergo a bone marrow biopsy at screening. If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to

confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated.

d. Schedule of Tumor Response Assessments for Rituximab-Containing Arms/Cohorts

Tumor response assessments will be performed every 3 months ($\pm$1 week) from the initiation of study treatment until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). The schedule of tumor assessments is independent of the study treatment dose schedule. For patients enrolled in rituximab-containing arms/cohorts, the schedule of tumor response assessments is detailed in Appendix A-1. As stated above, for all patients with DLBCL enrolled in a rituximab-containing arm/cohort, PET/CT scans are required during the screening period and at the 6-month tumor assessment timepoint.

The schedule for tumor response assessments for patients who proceed to crossover treatment is detailed in Appendix A-2.

Additional response assessments, after the final dose of study treatment, for patients who discontinue from study treatment (either initial or crossover treatment) for reasons other than progressive disease, will be performed as described in Appendix A-4.

Tumor assessments should also be performed within 30 days after the last study drug infusion (both initial and crossover treatment) at the treatment completion/early termination visit. Imaging scans are not required at the treatment completion/early termination visit if scans have been performed within the previous 8 weeks or if disease progression while receiving study treatment is documented.

If, at any time during the study, disease progression is suspected, a tumor assessment must be performed.

e. Schedule of Tumor Response Assessments for Obinutuzumab-Containing Cohorts

All patients with follicular NHL and DLBCL enrolled in obinutuzumab-containing cohorts are required to have a combined PET/CT scan at screening, after Cycle 4 of treatment, and at EOT. The schedule for tumor response assessments for patients enrolled in obinutuzumab-containing cohorts is detailed in Appendix A-3.

4.5.1.9 Exploratory Research

a. Tumor Tissue Samples

Required Tumor Tissue Samples

Tumor tissue samples will be used for central pathologic laboratory review of CD20, CD22, and CD79b expression. Additional studies to fulfill the exploratory objectives in Section 3.3.4 will be performed, including, but not limited, to the following:

- Messenger RNA (mRNA) expression profiling for signatures of NHL biology, including prognostic subpopulations (Alizadeh et al. 2000; Wright et al. 2003), target expression (CD20, CD22 and CD79b), and apoptotic response
- Tissue microarrays (TMAs) from cores taken from provided blocks for immunohistochemistry (IHC) and in situ hybridization (ISH) assessments for biomarker endpoints involved in response to chemotherapy including quantitation of Bcl-2 protein and genetic alterations of bcl-2 including gene rearrangements, amplifications, and t(14;18) translocations. Additional IHC markers may include those related to the tumor microenvironment.
- Tumor DNA to assess mutations that have been shown to be associated with NHL biology and activation of the B-cell receptor, including mutations in CD79b (Pasqualucci et al. 2011)

For patients who develop progressive disease and are eligible to receive crossover treatment (see Section 3.1.8), a biopsy of a safely accessible site of disease will be performed. Tumor tissue samples obtained at this timepoint will be used to assess changes in biology, target expression, and regulators of apoptosis as described above, which have occurred and may be linked to progression on initial study treatment.

Optional Tumor Tissue Samples (Requires Optional Research Informed Consent

For patients who provide informed consent, an optional tumor biopsy will be collected at time of progression from the following patients:

- Patients who develop disease progression following initial study treatment and do not proceed to receive crossover treatment
- Patients who develop disease progression on crossover treatment

Tumor tissue samples obtained at these timepoints will be used to assess changes in biology, target expression, and regulators of apoptosis, as described above, that have occurred and may be linked to progression on treatment.

b. Blood and Plasma Samples

A plasma sample will be collected prior to treatment.

Blood samples will be taken aligned with PK sampling to assess the pharmacodynamics response by monitoring circulating tumor DNA.

For patients who sign the Optional Research Informed Consent, an additional blood sample will also be taken prior to treatment.

The plasma and blood samples may be used for the assessment of specific tumor biologic markers, including proteins, circulating DNA, and microRNAs. The information obtained from these samples will enable a better understanding of the biology of NHL and disease prognosis, identify potential predictors of response to treatment with DCDT2980S, DCDS4501A, rituximab, and/or obinutuzumab, improve diagnostic assessments, and identify and characterize mechanisms of resistance to DCDT2980S or DCDS4501A and rituximab or obinutuzumab activity.

Because tumorigenesis is a multiple-step process linked to somatic events, any DNA analysis will focus on sporadic mutations specifically found in tumor tissue and not on inherited changes found in the whole body. For this purpose, some tumor-containing sections may be taken from the tissue block and used for the DNA extraction process. Assays on stored tissue samples may be performed at Genentech or at a central specialty laboratory.

4.5.1.10 Patient-Reported Outcomes

The MDASI (Cleeland et al., 2000; Appendix E) is a multi-symptom self-report measure for clinical and research use. The MDASI's 13 core-symptom items, plus an additional 4 items, for a total of 17 symptom items, include those found to have the highest frequency and/or severity in patients with various cancers and treatment types. These include pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling. Six additional items focus on the degree of interference of the aforementioned symptoms for a total of 23 items in the questionnaire.

PRO data will be elicited from all patients in this study (with the exception of Cohorts E, G, and H) to more fully characterize the clinical profile of study treatment. The MDASI PRO instrument will be supplied in the local language of each participating country. Electronic (handheld computers) will be used for the daily collection of symptoms derived from the MDASI.

4.5.2 Screening and Pretreatment Assessments

All screening evaluations must be completed and reviewed by the Genentech Medical Monitor or designated CRO Medical Monitor to confirm that patients meet all eligibility criteria and are approved for enrollment before the first infusion of study treatment. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site.

Screening and pretreatment tests and evaluations will be performed within 28 days preceding the day of the first dose of study treatment on Cycle 1 Day 1. Results of

standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 may be used; such tests do not need to be repeated for screening.

The availability of a patient's tumor tissue sample for studies (see Section 4.1.1 and Section 4.5.1.9) should be confirmed prior to Cycle 1 Day 1. Such specimens should consist of representative core biopsy in a paraffin block, which is the preferred method, or at least 15 unstained slides. Tumor specimens should be submitted with an accompanying pathology report and may be obtained at any time prior to entry to study.

Bone marrow biopsy and aspirate specimens are required at screening (see Section 4.5.1.8). For obinutuzumab-containing cohorts, bone marrow biopsy and aspirate are only required for follicular NHL patients. Unsuccessful attempts at obtaining marrow aspirates will not be considered a protocol deviation or violation.

Refer to the Study Flowchart provided in Appendix A-1 and A-3 for the schedule of screening and pretreatment assessments.

4.5.3 Assessments During Treatment

Study drug infusions (rituximab, obinutuzumab, DCDT2980S, or DCDS4501A) should occur on the scheduled 21-day (or 28-day) cycle but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ±1 day from the scheduled date, unless otherwise noted. Study visits starting in Cycle 3 should occur within ±2 days from the scheduled date, unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed prior to study drug infusion unless otherwise noted.

Local laboratory assessments may be performed within 72 hours preceding study drug administration on Day 1 of each cycle. Otherwise, laboratory samples should be drawn 0–4 hours before infusion. Results must be reviewed and the review documented prior to study drug administration.

Refer to the Study Flowchart provided in Appendix A-1 for the schedule of treatment period assessments. For patients enrolled in the obinutuzumab-containing cohorts, refer to the Study Flowchart provided in Appendix A-3.

4.5.4 Study Treatment Completion Visit

Patients who complete study treatment or discontinue from study treatment early will be asked to return to the clinic within 30 days after the last DCDT2980S, DCDS4501A, rituximab, or obinutuzumab infusion (whichever is later) for a study treatment completion visit. The visit at which response assessment shows progressive disease may be used as the early termination visit.

Refer to the Study Flowchart provided in Appendix A-1 for assessments to be performed at the treatment completion/early termination visit. For patients enrolled in the obinutuzumab-containing cohorts, refer to the Study Flowchart provided in Appendix A-3.

Assessments conducted at the treatment completion/early termination visit may be used for the purposes of re-screening to determine eligibility to receive crossover treatment (see Section 3.1.3 and Section 4.5.5).

4.5.5 Crossover Treatment Completion Visit

Patients who fulfill the criteria to receive crossover treatment (see Section 3.1.6) will have assessments during the crossover treatment period as described in Appendix A-2. The same guidelines regarding scheduling of assessments for treatment with initial study treatment as detailed in Section 4.5.3 will apply to crossover treatment.

Patients who proceed to receive crossover treatment will have on-treatment assessments as described in Appendix A-2.

Patients who complete the crossover treatment (approximately 1 year/17 cycles) or discontinue from crossover treatment early will be asked to return to the clinic within 30 days after the last DCDT2980S, DCDS4501A, or rituximab infusion (whichever is later) for a crossover treatment completion/early termination visit. The visit at which response assessment shows disease progression on crossover treatment may be used as the early termination visit.

Refer to Appendix A-2 for assessments to be performed at the treatment completion/early termination visit.

4.5.6 Follow-Up Assessments

Ongoing adverse events thought to be related to DCDT2980S, DCS4501A, rituximab, or obinutuzumab will be followed until the event has resolved to baseline (pre-treatment) grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the adverse event.

Patients will be followed after the last dose of study treatment (either initial study treatment or crossover treatment) for safety outcomes. Such follow-up will require an assessment (per verbal report, at minimum) of any adverse events and serious adverse events for 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy, whichever occurs first.

4.5.6.1 Follow-Up Assessments for Rituximab-Containing Regimens

Patients who discontinue from study treatment (either initial study treatment or crossover treatment) for reasons other than progressive disease will be followed for response for up to 1 year after the last infusion of study treatment or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Response assessments should occur approximately every 2–3 months following the last infusions of DCDT2980S, DCDS4501A, or rituximab. Post-treatment assessments are described in Appendix A-4.

Following discontinuation of study treatment, patients will be followed for survival approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination.

4.5.6.2 Follow-Up Assessments for Obinutuzumab-Containing Regimens

Patients who discontinue from study treatment for reasons other than progressive disease will be followed for response for up to 2 years after the last infusion of study treatment or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Response assessments should occur approximately every 2–3 months following the last infusions of DCDS4501A or obinutuzumab for the first year after completion of treatment, then every 6 months for the second year after completion of treatment. Post-treatment assessments are described in Appendix A-5.

Following discontinuation of study treatment, patients will be followed for survival approximately every 6 months until death, loss to follow-up, withdrawal of consent, or study termination.

4.6 PATIENT DISCONTINUATION

4.6.1 Discontinuation from Treatment

Patients may discontinue study treatment early for reasons other than disease progression, such as patient/investigator choice or unacceptable toxicity. The reasons for early discontinuation of treatment must be documented on the appropriate eCRF. Patients may continue treatment with either DCDT2980S/DCDS4501A or rituximab alone following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

Patients who discontinue study treatment early due to toxicity should continue to be followed until resolution of toxicity as scheduled.

Refer to Section 4.5.4 and Section 4.5.5 for assessments that are to be performed for patients who discontinue from the study during the study treatment period.

4.6.2 Discontinuation from Study

Patients must be discontinued from the study if they experience disease progression as defined using response and progression criteria in Appendix C. Patients can continue crossover treatment following documentation of the first progressive disease event but must be discontinued from the study if they experience a second progressive disease event on the crossover treatment.

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study, for reasons of noncompliance (e.g., missed doses or missed visits) or pregnancy or if the investigator determines it is in the best interest of the patient.

Refer to Section 4.5.4 and Section 4.5.5 for assessments that are to be performed for patients who prematurely discontinue from the study during the treatment period.

4.7 STUDY DISCONTINUATION

Genentech has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

4.8 POST-TRIAL ACCESS

Genentech does not have any plans to provide DCDT2980S, DCDS4501A, rituximab, obinutuzumab, or other study interventions to patients after the conclusion of the study or if the study is terminated or for patients who withdraw early from the study or complete their study treatment. Genentech will evaluate the appropriateness of continuing to provide DCDT2980S, DCDS4501A, rituximab, or obinutuzumab to study patients after evaluating the safety and activity data from the study.

4.9 ASSAY METHODS

4.9.1 Total DCDT2980S/DCDS4501A Antibody ELISA

Total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) will be measured in serum samples using validated ELISAs.

4.9.2 Antibody-Conjugated MMAE (MMAE Affinity Capture Enzyme-Release LC/MS-MS)

acMMAE (a measure of MMAE conjugated to DCDT2980S/DCDS4501A) will be measured in plasma samples using validated affinity capture enzyme-release liquid chromatography–tandem mass spectrometry (LC-MS/MS) assays.

4.9.3 Free MMAE LC-MS/MS

Free MMAE will be measured in plasma samples using a validated electrospray LC-MS/MS method.

4.9.4 Rituximab ELISA

Rituximab will be measured in serum samples using a validated ELISA.

4.9.5 Obinutuzumab ELISA

Obinutuzumab will be measured in serum samples using a validated ELISA.

4.9.6 Anti-Therapeutic Antibody

ATAs against DCDT2980S and DCDS4501A in serum samples will be measured using validated bridging antibody ELISAs and characterized by competitive binding assays.

ATAs against obinutuzumab in serum samples will be measured using a validated bridging antibody ELISA and characterized by a competitive binding assay.

4.9.7 Biomarker Assays

Tumor tissue assessment of biomarkers will be assayed using IHC, ISH, qPCR gene expression profiling using microarray and mutation detection assays. Circulating Tumor DNA (ctDNA) in plasma samples may be assessed using a next generation sequencing approach (CAPP-Seq) to detect and quantitate lymphoma specific markers.

4.10 STATISTICAL METHODS

The final analysis will be based on patient data collected until all patients discontinue from the study or the study is terminated by the Sponsor, whichever occurs first. The analyses will be based on the safety evaluable population, defined as patients who received at least one dose of study treatment. All summaries will be presented according to the disease-specific cohort, treatment group, and assigned dose level.

4.10.1 Analysis of the Conduct of the Study

Enrollment, major protocol violations, and reasons for discontinuations from the study will be summarized.

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, duration of malignancy, and baseline ECOG Performance Status, will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables. All summaries will be presented overall and by treatment group, assigned dose level, and disease-specific cohort.

Study drug administration data will be listed by the disease-specific cohorts described in Section 3.1.1 and Section 3.1.2. Any dose modifications will be flagged. Means and standard deviations will be used to summarize the total doses of DCDT2980S,

DCDS4501A, rituximab, and obinutuzumab received. All summaries will be presented by treatment group, assigned dose level, and disease-specific cohort.

4.10.2 Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, and changes in vital signs. All patients who receive any amount of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab will be included in the safety analysis and will be assigned to the treatment group on the basis of the study treatment received. Patients who have dose level changes from the initial assigned dose level will be summarized by the initial assigned dose level of DCDT2980S or DCDS4501A.

All adverse event data will be listed by study site, patient number, treatment group, disease-specific cohort, and cycle. All adverse events occurring on or after treatment on Day 1 of Cycle 1 will be summarized by mapped terms, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade. In addition, all serious adverse events, including deaths will be listed separately and summarized.

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to DCDT2980S and DCDS4501A will be summarized.

4.10.3 Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum concentrations of total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) and rituximab or obinutuzumab and plasma concentrations of acMMAE and free MMAE versus time data will be tabulated and plotted by NHL disease subtype (relapsed or refractory follicular NHL or DLBCL). The pharmacokinetics of the above analytes will be summarized by estimating the appropriate PK parameters (e.g., AUC, C_{max}, CL, V_{ss}, and $t_{1/2}$). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and range). Non-compartmental, compartmental, and/or population methods will be used, as data allow.

Exposure-response (safety and efficacy) analysis may be conducted with use of PK data and available drug effect (e.g., imaging, measures of tumor burden) and toxicity (e.g., clinical pathology) data, at the sponsor's discretion.

In addition, population PK methods may be employed to manage sparse data and to investigate the effects of certain covariates on the pharmacokinetics of DCDT2980S and DCDS4501A, as data allow, and at the sponsor's discretion.

4.10.4 Activity Analyses

Best overall response, duration of response, and PFS will be listed for all patients.

ORR from the initial study treatment will be calculated on the basis of data from patients who received study treatment. Objective response is defined as CR or PR as determined by the investigator, on the basis of physical examinations, radiographic scans, and bone marrow examinations, using modified response criteria for NHL (Cheson et al. 2007; see Appendix C) and confirmed by repeat assessments ≥4 weeks after initial documentation. Any patient with insufficient data to determine response will be classified as a non-responder.

For patients *in the rituximab-containing arms/cohorts* with DLBCL, primary assessment of tumor response will be based on diagnostic imaging scans—for example, CT and/or MRI scans and PET/*CT* scans. For patients with FL enrolled in the rituximab-containing arms/cohorts, primary assessment of response will be based on CT scans only; the assessment of response in patients with FL based on PET/*CT* scans will be performed for exploratory purposes only.

For patients in the obinutuzumab-containing cohorts, primary response assessment for patients with DLBCL or FL will be based on PET/CT scans using the updated 2014 Lugano Response Criteria as determined by an IRC. Patients in Cohorts E, G, and H will be evaluated with a PET/CT scan at screening, between Cycle 4 Day 15 and Cycle 5 Day 1, and at EOT (6–8 weeks after completing treatment). The efficacy analysis for these cohorts will, therefore, be different from the analysis for Arms A–B and Cohorts C–D (Cheson, et al 2014) (see Appendix C-2). Subsequent imaging can be CT only. Responses to study treatment will also be based on investigator assessments.

Among patients with an objective response, duration of response will be defined as the time from the initial documentation of a CR or PR to the time of disease progression or death. If a patient does not experience death or disease progression before the end of the study, duration of response will be censored at the day of the last tumor assessment.

For the randomized portion of the study (Arms A and B), PFS is defined as the time from the date of randomization to the date of disease progression or death from any cause, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the date of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. For the non-randomized portion of the study (Cohorts C through H), PFS is defined as the time from the date of study enrollment to the date of disease progression or death from any cause, whichever occurs first.

For the randomized portion of the study (Arms A and B), OS is defined as the time from the date of randomization to the date of death from any cause. For the non-randomized portion of the study (Cohorts C through H), OS is defined as the time from the date of study enrollment to date of death from any cause.

4.10.5 Exploratory Analyses

Assay results of possible predictive markers will be listed by treatment group and response status.

Frequencies and percentages of missing data for the PRO endpoints will be reported. Dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) will be summarized

Summary statistics of the MDASI items, scales, and their changes from baseline will be calculated at each assessment timepoint. The mean, standard error, and median of the absolute scores and the mean changes from baseline (and 95% CI) within and between study arms will be reported for the MDASI scales and single items, as well as the weekly averages of the worst symptom rating. For change scores in the MDASI from baseline, patients without baseline scores will not be included in the analyses. Line charts depicting the means and mean changes of subscales over time will be also provided.

Repeated measures mixed-effects models will explore MDASI subscale scores with a baseline score and appropriate covariates added, as appropriate.

4.10.6 Handling of Missing Data

For the endpoint of objective response, patients without a post-baseline tumor assessment will be considered non-responders in the all-treated population analysis.

For duration of response and PFS, data from patients who are lost to follow-up will be included in the analysis as censored observations on the last date that the patient is known to be progression free, defined as the date of the last tumor assessment, or, if no tumor assessments were performed, as the date of last study treatment plus 1 day.

Compliance to PRO data collection will be reported with summary statistics, including frequencies of reasons for non-compliance such as patient refusal to complete PRO data collection.

4.10.7 Determination of Sample Size

For the randomized portion of the study (Arms A and B), a target of 120 patients will be enrolled in two separate cohorts of patients (40 in the follicular NHL cohort and 80 in the DLBCL cohort). The randomized portion of this study is non-comparative in nature. No formal hypothesis testing is planned to compare the treatment arms. Moreover, there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms. Genentech has judged the proposed sample size to provide sufficient

precision in estimating the anti-tumor activity of DCDT2980S combined with rituximab or DCDS4501A combined with rituximab as measured by objective response. For example, with the assumption of an observed response rate of 40%, a 90% confidence interval for the response rate would be approximately 22%–58% (i.e., 40% ± 18%) for the follicular NHL cohort and approximately 27%–53% (i.e., 40% ± 13%) for the DLBCL cohort. With 40 patients, there is an 87% chance of observing at least one adverse event with a true incidence of 5%.

For the non-randomized portions of the study (Cohorts C and D), approximately 20 patients will be enrolled into each arm, for a total of 40 patients. With 20 patients under an observed response rate of 40%, the exact Clopper-Pearson 90% confidence interval for the response rate would be 22%–61%. With respect to the assessment of safety based upon a sample size of 20 patients, the chance of observing at least one adverse event with a true incidence of 10% is 88%.

For the obinutuzumab safety run-in cohort (Cohort E), 6 patients will be enrolled. For the obinutuzumab expansion cohorts (Cohorts G and H), 40 patients with follicular NHL, and 40 patients with DLBCL will be enrolled at the RP2D to further evaluate safety and efficacy of the combination. Table 3 provides asymptotic 90% confidence intervals for the true probability of response for a range of observed proportions based upon a sample of 40 patients. A sample size of 40 patients is deemed sufficient to provide adequate precision on the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting rate of 45% assuming observed response rates of approximately 60% or higher (~24 responders observed among 40 patients).

Table 3 Potential 90% Interval Estimates for the True Response Probability

Observed Proportion of Responders	90% Confidence Interval for True Probability of Response
0.50	(0.37, 0.63)
0.60	(0.47, 0.73)
0.65	(0.53, 0.77)
0.70	(0.58, 0.82)
0.75	(0.64, 0.86)

Therefore, up to 246 patients may be enrolled in this study.

4.11 DATA QUALITY ASSURANCE

The data will be collected via EDC using eCRFs. The site will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The CRO will be responsible for the data management of this trial, including quality checking of the data.

Genentech will perform oversight of the data management of this trial. Genentech will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central Laboratory data and other electronic data will be sent directly to Genentech, using Genentech's standard procedures to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Genentech and records retention for the study data will be consistent with Genentech's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and physical examinations and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

Genentech or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Genentech or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Genentech or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central Institutional Review Board/ethics committee (IRBs/ECs, except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

5.1.1 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the baseline hematologic malignancy (i.e., leukemia or lymphoma) that were not present prior to the AE reporting period (see Section 5.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., medication washout, no treatment run-in, or invasive procedures such as biopsies)
- Preexisting medical conditions other than the disease under study that are judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

5.1.2 Serious Adverse Event

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the investigator (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

5.1.3 *Protocol-Defined Adverse Events of Special Interest/Non-Serious Expedited Adverse Events*

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions), irrespective of regulatory seriousness criteria. Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.1.6; treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN [of which $\geq 35\%$ is direct bilirubin])
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Tumor lysis syndrome (TLS) of any grade, irrespective of causality
- *Secondary malignancies*

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 5.1) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

5.2.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

After initiation of study drug (the Genentech product[s] or other IMP), all new AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment *with the exception of second malignancies* (see Section 5.6). *Second malignancies will be recorded indefinitely (even if the study has ended) and irrespective of new anti-lymphoma treatment (NALT).*

5.2.2 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation timepoints should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.2.3 Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity, and causality.

Table 4 provides guidance for grading AE severity, and Table 5 provides guidance for assessing the causal relationship to the investigational product(s).

The AE grading (severity) scale found in the NCI CTCAE v4.0 will be used for AE reporting

Table 4 Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Transient or mild discomfort (<48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

AE=adverse event; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; SAE=serious adverse event.

The NCI CTCAE v4.0 can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE (see Section 5.1.2).

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.

To ensure consistency of causality assessments, investigators should apply the following general guidelines:

Table 5 Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

AE=adverse event; SAE=serious adverse event.

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

5.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

5.3.1 Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF. Avoid colloquialisms and abbreviations.

There is one eCRF page for recording AEs or SAEs.

Only one medical concept should be recorded in the event field on the Adverse Event eCRF.

5.3.1.1 Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

5.3.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

5.3.1.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation timepoints. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation timepoints and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF.

5.3.1.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management, e.g., concomitant medication, will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Specific to this study, lymphopenia and leukopenia due to lymphopenia of any grade are expected PD effects of study drug and therefore are not considered to be AEs. However, complications of lymphopenia (e.g., infections) will need to be reported as AEs. In addition, because monocytopenia is not reportable and neutropenia is already being monitored and reported as an AE, leukopenia does not need to be reported as a distinct AE.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

5.3.1.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (including a diagnostic evaluation not mandated in this protocol) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.1.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or a non-serious adverse event of special interest (see Section 5.4.2)

5.3.1.7 Deaths

Deaths that occur during the protocol-specified AE reporting period (see Section 5.2.1) that are attributed by the investigator solely to progression of lymphoma will be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of attribution, will be recorded on the Adverse Event eCRF and expeditiously reported to the Sponsor.

When recording a death on an eCRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” on the Adverse Event eCRF.

5.3.1.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History eCRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.1.9 Worsening of Baseline Hematologic Malignancy

Worsening and/or progression of the baseline hematologic malignancy (e.g. leukemia or lymphoma) should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

5.3.1.10 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

5.3.1.11 Pregnancy

If a female patient becomes pregnant while receiving the study drug or within 12 months after the last dose of study treatment, a Pregnancy Report eCRF should be completed within 24 hours of learning of the pregnancy. A pregnancy report will automatically be generated and sent to Genentech's Drug Safety Department or its designee. Pregnancy should not be recorded on the Adverse Event eCRF.

Male patients must also be instructed to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the last dose of study drug. If such an event occurs, it should be reported as described below.

Abortion, whether therapeutic or spontaneous, should always be classified as an SAE (as the Sponsor considers these medically significant), recorded on an Adverse Event eCRF, and expeditiously reported to the Sponsor (see Section 5.4.2).

Any congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and expeditiously reported to the Sponsor (see Section 5.4.2).

After the study period, abortions, congenital anomalies/birth defects, and pregnancy outcomes should still be reported expeditiously to the Sponsor.

In the event the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee within 24 hours of learning of the pregnancy, at the fax numbers listed in Section 5.4.2.

a. Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 1 working day after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee within 24 hours of learning of the pregnancy, at the fax numbers listed in Section 5.4.2.

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

5.4.1 Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an eCRF within 24 hours as described in Section 5.4.2.

Medical Monitor Contact Information for sites in North America:

Medical Monitor: [redacted], M.D.
Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

For sites outside of North America, local contact details and numbers for safety issues and safety reporting will be provided in the study reference binder.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of SAEs and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the EDC system. A report will be

generated and sent to the Sponsor's Safety Risk Management department by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Sites in North America:

Fax No.: [redacted]

Sites in Europe:

Fax No.: [redacted]

Relevant follow-up information should be submitted to Genentech's Drug Safety Department or its designee as soon as it becomes available and/or upon request.

5.5 TYPE AND DURATION OF FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV).

For some SAEs, the Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

5.6 POST-STUDY ADVERSE EVENTS

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt to be related to prior study treatment. *Second malignancies will be recorded indefinitely (even if the study has been closed) and irrespective of NALT.* The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to Genentech Drug Safety on the

study eCRF. If the study eCRF is no longer available, the investigator should report the event directly to Genentech Drug Safety either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided below.

Canada:

Fax No.: (905) 542−5864

Email: mississauga.drug_safety@roche.com

France:

Fax No: 33 147617777

Email: neuilly.drug_safety@roche.com

Germany:

Fax No.: [redacted]

Email: grenzach.drug_safety@roche.com

Italy:

Fax No.: [redacted]

Email: monza.drug_safety@roche.com

Netherlands:

Fax No.: [redacted]

Email: woerden.drug_safety@roche.com

United States:

Fax No.: [redacted]

Email: us_drug.safety@gene.com

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with Genentech or a Genentech representative:

- FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

  The names of any subinvestigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.

- Current curricula vitae and evidence of licensure of the Principal Investigator and all subinvestigators

- Complete financial disclosure forms for the Principal Investigator and all subinvestigators listed on the FDA Form 1572
- Federalwide Assurance number or IRB statement of compliance
- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form

  Genentech or its designee must review any proposed deviations from the sample Informed Consent Form.
- Current laboratory certification of the laboratory performing the analysis (if other than a Genentech-approved central laboratory), as well as current references ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator Brochure Receipt signed and dated by the Principal Investigator
- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable) , IRB/EC approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator
- Canada only when applicable: original Qualified Investigator Undertaking Form, signed by each Canadian investigator involved in the study
- For global studies, list documents as appropriate for additional countries.

6.2 STUDY COMPLETION

The following data and materials are required by Genentech before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- All laboratory certifications for laboratories performing the analysis (is other than Genentech-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and subinvestigator, FDA Form 1572 for each site)

- A signed and dated Protocol Amendment Acceptance Form(s) [if applicable]
- Updated financial disclosure forms for the Principal Investigator and all subinvestigators listed on the FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

6.3 INFORMED CONSENT FORM

Genentech's Sample Informed Consent Form will be provided to each site. Genentech or its designee must review and approve any proposed deviations from the Sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the Consent Forms during their participation in the study. The final IRB/EC-approved Consent Forms must be provided to Genentech for regulatory purposes.

The Consent Forms must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved Informed Consent Form must be provided to Genentech for regulatory purposes.

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval, and other processes outlined above apply except that IRB/IEC review and approval may not be required per study site policies.

Optional Research Informed Consent

Informed consent for the collection and use of fresh tumor tissue at time of progression for optional research described in Section 4.5.1.10 will be documented in a section of the main Informed Consent Form. This section provides patients with the option to authorize

the collection and use of these samples and personal health information for additional research purposes. Agreement to participate in the optional research (by checking the appropriate box in this section of the main Informed Consent Form) is not required for enrollment in the trial but is required prior to any optional research sample collection. Optional consent may be withdrawn at any time by the patient.

6.4 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from Genentech. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's Study File.

6.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Genentech representative to inspect site facilities and equipment, study source data, patients' medical records, and eCRFs. The Principal Investigator will oversee all aspects of the conduct of this protocol and permit Genentech monitors/representatives and collaborators, the FDA, other regulatory agencies, Institutional Review Boards, and the respective national or local health authorities to inspect facilities and records relevant to this study.

6.6 ELECTRONIC CASE REPORT FORMS

eCRFS are to be completed using the [redacted] EDC system. Sites will receive training for appropriate eCRF completion. eCRFs will be submitted electronically to Genentech and should be handled in accordance with instructions from Genentech.

All eCRFs should be completed by designated, trained personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

In addition, at the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

6.7 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing SDV to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where original patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, certified accurate and complete copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Original source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to all applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

6.8 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

In collaboration with the study monitor, Genentech's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

6.9 STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by Genentech. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Genentech with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

6.10 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

6.11 RETENTION OF RECORDS

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of Genentech. Written notification should be provided to Genentech prior to transferring any records to another party or moving them to another location.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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Appendix A–1
Study Flowchart: Initial Study Treatment (Arms A–B, Cohorts C–D)

Cycle	Screening	Treatment Period											Treatment Completion/Early Termination Visit [c]	Safety and Survival Follow-Up [d]
		Cycle 1				Cycles 2–4				Cycles 5–17				
Day(s)[a] Assessment	–28 to –1	1 [b]	2	8	15	1 [b]	2	8	15	1 [b]	2	15		
Written informed consent [e]	x													
Review inclusion/exclusion criteria	x													
Medical history and demographics	x													
Height (screening only) and weight	x	x				x				x				
Vital signs	x	x [f]	x [f]	x	x	x [f]	(x) [f]	x	x	x [f]	(x) [f]	x	x	
ECOG Performance Status	x	x		x	x	x		x	x	x			x	
B symptoms [g]	x	x				x				x			x	
Complete physical examination [h]	x													
Targeted physical examination [i]		x	x	x		x	(x)			x	(x)		x	
Concomitant medications	x	x	x	x	x	x	(x)	x	x	x	(x)	x	x	
Adverse events [j]	x	x	x	x	x	x	(x)	x	x	x	(x)	x	x	x
MDASI PRO [k]		Day 1–8 of Cycles 1–8												
12-lead electrocardiogram [l]	x	Refer to Footnote “l”											x	
Tumor assessments [m]	x	Every 3 months											x	
PET/*CT* scan (required for DLBCL; optional for FL) [m]	x	6-month tumor assessment and as clinically indicated												
Rituximab infusion		x				x				x				
DCDT2980S or DCDS4501A infusion [n]			x			x	(x)			x	(x)			

Appendix A–1 (cont.)
Study Flowchart: Initial Study Treatment (Arms A–B, Cohorts C–D)

Cycle	Screening	Treatment Period											Treatment Completion/Early Termination Visit [c]	Safety and Survival Follow-Up [d]
		Cycle 1				Cycles 2–4				Cycles 5–17				
Day(s)[a] Assessment	–28 to –1	1 [b]	2	8	15	1 [b]	2	8	15	1 [b]	2	15		
Local Laboratory Assessments														
HBV and HCV screening [o]	x													
Hematology [p]	x	x		x	x	x		x	x	x		x	x	
Serum chemistry [q]	x	x		x	x	x		x	x	x		x	x	
Hemoglobin A1c	x									Cycle 5 Day 1				
Total IgA, IgG, IgM	x									Cycle 8 Day 1			x	
Coagulation (aPTT, PT, and INR)	x													
Pregnancy test [r]	x	Within 10 days of Day 1 of Cycles 3, 6, 9, 12, and 15											x	
Bone marrow biopsy [s]	x	Perform to confirm CR if positive for disease at screening or if clinically indicated												
Central Laboratory Assessments														
Leukocyte immunophenotyping (FACS) [t]		Day 1 of Cycle1, Cycle 4, Cycle 8 and Cycle12											x	
Tumor tissue sample [u]	x												x	
Exploratory plasma (required) and blood (optional) sample [v]	x													
DCDT2980S or DCDS4501A and rituximab pharmacokinetic sampling [w]	Refer to Appendix B-1 and Appendix B-2													
Serum sample for anti-DCDT2980S or anti-DCDS4501A antibody [x]														

Appendix A–1 (cont.)
Study Flowchart: Initial Study Treatment (Arms A–B, Cohorts C–D)

AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CR = completed response; CT = computed tomography; DLBCL = ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; FL = follicular lymphoma; GGT = γ-glutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; MDASI = MD Anderson Symptom Inventory; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography; PCR = polymerase chain reaction; PT = prothrombin time; QLQ = Quality of Life Questionnaire; SAE = serious adverse event; (x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle —refer to footnote 'n' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 1 year (approximately 17 cycles on an every-21-day schedule) and may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ±1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 3 should occur within ±2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DCDT2980S or DSDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 1 year of total study treatment (approximately 13 cycles).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding rituximab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] Perform within 30 days after the last infusion of DCDT2980S, DCDS4501A, or rituximab. The visit at which response assessment shows progressive disease may be used as the early termination visit. Assessments during the treatment completion/early termination visit may be applied to assessments required to determine eligibility to receive crossover treatment. Patients enrolled into Cohorts C and D are not eligible to receive crossover treatment.

[d] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report from the patient, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-4 for schedule of assessments during the post-treatment period. Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

[e] Informed consent form(s) must be signed by the patient before any study-specific procedures are performed.

[f] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2 of the protocol.

[g] Defined as unexplained weight loss > 10% over previous 6 months, fever (> 38°C/100.4°F), and/or drenching night sweats.

[h] Complete physical examination includes all systems described in Section 4.5.1.3.

[i] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDT2980S or DCDS4501A dosing on Day 2 of each cycle if given on separate days from rituximab only if clinically indicated—for example, to follow- up on signs or symptoms observed from the examinations performed on Day 1.

Appendix A–1 (cont.)
Study Flowchart: Initial Study Treatment (Arms A–B, Cohorts C–D)

[j] After informed consent is obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs and SAEs, regardless of attribution, must be reported until 30 days following the last administration of study drug or until the patient receives another anti-cancer therapy, whichever occurs first. After this period, investigators should report only SAEs considered related to prior study treatment *with the exception of second malignancies. Second malignancies will be recorded indefinitely (even if the study has ended) and irrespective of NALT.*

[k] Treatment and disease associated symptoms using the MDASI questionnaire will be collected on hand-held computer devices (see Section 4.5.1.10).

[l] Twelve-lead digital electrocardiogram (ECG) measurements must be obtained in triplicate (with immediately consecutive ECGs obtained until three evaluable ECGs are recorded) at the timepoints specified in Section 4.5.1.5. Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction. The evaluating physician should determine the clinical significance of any abnormal ECGs.

[m] Tumor assessments should be performed at screening and every 3 months while receiving study treatment regardless of study treatment dose schedule. Tumor assessments should also be performed within 30 days after the last study drug infusion as part of the treatment completion/early termination visit. Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C-1). For DLBCL patients, a PET scan is required during screening, at the 6-month tumor assessment timepoint and as clinically indicated. For patients with FL, a PET scan is not required but may be obtained based on physician preference and if permitted by local health authorities. Refer to Section 4.5.1.8 for complete details.

[n] Administer DCDT2980S or DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related AEs. For Cycle 1 and Cycle 2, DCDT2980S or DCDS4501A should be administered on the day after rituximab is administered—for example, Day 2 if rituximab is given on Day 1, or Day 3 if rituximab is given as a split dose on Days 1 and 2. In the absence of any infusion-related AEs, rituximab followed by DCDT2980S or DCDS4501A may be administered on the same day in each cycle starting with Cycle 3. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[o] HBsAg, HBcAb, and Hep C Ab serology required. If HBcAb or HCV antibody is positive, HBV/HCV DNA by PCR is required.

[p] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[q] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid. Serum GGT levels will be required at screening only.

[r] A serum pregnancy test should be performed for women of childbearing potential within 14 days prior to receiving first study treatment. In addition, a urine pregnancy test must also be performed within 10 days prior to Day 1 of Cycles 3, 6, 9, 12, and 15, and at the treatment completion/early termination visit unless patient receives crossover treatment, in which case follow the schedule of pregnancy testing outlined in Appendix A-2. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[s] Bone marrow biopsy for morphology (aspirates for morphology and/or flow studies are optional) is required at screening. Bone marrow biopsy for morphology is required at screening and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated. Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.

[t] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[u] Availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, obtained at any time prior to entry to study. A biopsy of a safely accessible site of disease, defined as requiring only local anesthesia and in general excluding brain, lungs or any internal organs that may subject patients to significant risk, is required for patients who proceed to crossover treatment; if no such lesion exists, then a biopsy is not required.

[v] All patients who have successfully passed screening and are fully eligible for the study will have a 10-mL plasma sample taken for exploratory research.

[w] Pharmacokinetic serum and plasma samples should be drawn according to the schedule provided in Appendices B-1 and B-2.

[x] Whole blood samples for assessment of anti-DCDT2980S or anti-DCDS4501A antibodies in serum will be drawn according to the schedule provided in Appendices B-1 and B-2.

Appendix A–2
Study Flowchart: Crossover Treatment (Patients Randomized to Arms A or B Only)

Cycle	Treatment Period											Crossover Treatment Completion/Early Termination Visit [c]	Safety and Survival Follow-Up [d]
	Cycle 1b				Cycles 2b–4b				Cycles 5b–17b				
Day(s) [a] Assessment	1 [b]	2	8	15	1 [b]	2	8	15	1 [b]	2	15		
Weight	x				x				x				
Vital signs	x [e]	(x) [e]	x	x	x [e]	(x) [e]	x	x	x [e]	(x) [e]	x	x	
ECOG Performance Status	x		x	x	x		x	x	x			x	
B symptoms [f]	x				x				x			x	
Targeted physical examination [g]	x	(x)	x		x	(x)			x	(x)		x	
Concomitant medications	x	(x)	x	x	x	(x)	x	x	x	(x)	x	x	
Adverse events [h]	x	(x)	x	x	x	(x)	x	x	x	(x)	x	x	x
Tumor assessments [i]	Every 3 months											x	
Rituximab infusion	x				x				x				
DCDT2980S or DCDS4501A infusion [j]	x	(x)			x	(x)			x	(x)			
Local Laboratory Assessments													
Hematology [k]	x		x	x	x		x	x	x		x	x	
Serum chemistry [l]	x		x	x	x		x	x	x		x	x	
Total IgA, IgG, IgM									Cycle 8b Day 1			x	
Pregnancy test [m]	Day 1 of Cycles 3b, 6b, 9b, 12b, and 15b											x	
Bone marrow biopsy [n]	Perform to confirm CR if positive for disease at screening or if clinically indicated												
Central Laboratory Assessments													
Leukocyte immunophenotyping (FACS) [o]	Day 1 of Cycle 4, 8, and 12											x	
Tumor biopsy/sample												x [p]	

Appendix A–2 (cont.)
Study Flowchart: Crossover Treatment (Patients Randomized to Arms A or B Only)

AE = adverse event; AL = alanine aminotransferase; AST = aspartate aminotransferase; CR = complete response; LDH = lactate dehydrogenase; SAE = serious adverse event; (x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle—refer to footnote 'j' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 1 year (approximately 17 cycles) and may be given up to ± 2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ± 1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 3 should occur within ± 2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DCDT2980S or DSDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 1 year of total study treatment (approximately 13 cycles).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding rituximab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] Perform within 30 days after the last infusion of DCDT2980S, DCDS4501A or rituximab. The visit at which response assessment shows progressive disease may be used as the early termination visit.

[d] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-4 for schedule of assessments during the post-treatment period. Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

[e] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2 of the protocol.

[f] Defined as unexplained weight loss > 10% over previous 6 months, fever (> 38°C/100.4°F), and/or drenching night sweats.

[g] Targeted physical examinations should be limited to systems of clinical relevance and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDT2980S or DCDS4501A dosing on Day 2 of each cycle if given on separate days from rituximab only if clinically indicated, e.g. to follow -up on signs or symptoms observed from the examinations performed on Day 1.

[h] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. *Investigators should report second malignancies indefinitely (even if the study has ended) and irrespective of NALT.* Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-4 for schedule of assessments

during the post-treatment period.

[i] Tumor assessments should be performed at screening and every 3 months while receiving study treatment. Tumor assessments should also be performed 28–56 days after the last study drug infusion as part of the crossover treatment completion/early termination visit. Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C-1).

[j] Administer DCDT2980S or DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related adverse events. For Cycle 1b and Cycle 2b, DCDT2980S or DCDS4501A should be administered on the day after rituximab is administered, e.g., Day 2 if rituximab is given on Day 1, or Day 3 if rituximab is given as a split dose on Days 1 and 2. In the absence of any infusion-related adverse events, rituximab followed by DCDT2980S or DCDS4501A may be administered on the same day in subsequent cycles starting with Cycle 3b. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle, but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[k] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[l] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT), AST, alkaline phosphatase, LDH, and uric acid.

[m] A serum pregnancy test should be performed for women of childbearing potential within 14 days prior to receiving first study treatment. In addition, a serum or urine pregnancy test must be performed within 10 days prior to Day 1 of Cycles 3, 6, 9, 12, and 15 and at the crossover treatment completion/early termination visit. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[n] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[o] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[p] Optional tumor biopsy of a safely accessible site of disease, defined as requiring only local anesthesia and in general excluding brain, lungs or any internal organs that may subject patients to significant risk. Tumor samples will be used for research purposes.

Appendix A–3
Study Flowchart for Obinutuzumab-Containing Cohorts (E, G–H): Initial Study Treatment

Cycle	Screening	Treatment Period									Treatment Completion/ Early Termination Visit[c]	End of Treatment Response Assessment (after Cycle 8 Day 1 or last study treatment +6–8 weeks)	Safety and Survival Follow-Up [d]
		Cycle 1				Cycles 2–4		Cycle 4	Cycles 5–8				
Day(s)[a] Assessment	–28 to –1	1[b]	2	8	15	1[b]	2	15[c]	1[b]	2			
Written informed consent[e]	x												
Review inclusion/exclusion criteria	x												
Medical history and demographics	x												
Height (screening only) and weight	x	x				x			x				
Vital signs	x	x[f]	x[f]	x[f]	x[f]	x[f]	(x)[f]		x[f]	(x)[f]	x		
ECOG Performance Status	x	x		x	x	x			x		x		
Complete physical examination [g]	x												
Targeted physical examination [h]		x	x	x		x	(x)		x	(x)	x		
Concomitant medications	x	x	x	x	x	x	(x)		x	(x)	x		
Adverse events [i]	x	x	x	x	x	x	(x)		x	(x)	x		x
12-lead electrocardiogram[j]	x	Refer to Footnote “j”									x		
Tumor/Assessment (PET/CT scan (required for DLBCL and FL) [k]	x							x[m]				x[m]	

Appendix A-3 (cont.)
Study Flowchart for Obinutuzumab-Containing Cohorts (E, G–H): Initial Study Treatment

Obinutuzumab infusion		x		x	x	x			x				
DCDS4501A infusion [l]			x			x	(x)		x	(x)			
Local Laboratory Assessments													
HBV and HCV screening [m]	x												
Hematology [n]	x	x		x	x	x			x		x		
Serum chemistry [p]	x	x		x	x	x			x		x		
Hemoglobin A1c	x								Cycle 5 Day 1				
Total IgA, IgG, IgM	x								Cycle 8 Day 1		x		
Coagulation (aPTT, PT, and INR)	x												
Pregnancy test [p]	x	Within 10 days of Day 1 of Cycles 3, 6									x		
Bone marrow biopsy [q]	x[q]	Perform to confirm CR if positive for disease at screening or if clinically indicated											
Central Laboratory Assessments													
Leukocyte immunophenotyping (FACS) [t]		Day 1 of Cycle1, Cycle 4, and Cycle 8									x		
Tumor tissue sample [u]	x										x		
Exploratory plasma sample [v]	x												
DCDS4501A and obinutuzumab pharmacokinetic sampling[w]	Refer to Appendix B-3												
Serum sample for anti-DCDS4501A antibody[x]	Refer to Appendix B-3												

Appendix A-3 (cont.)
Study Flowchart for Obinutuzumab-Containing Cohorts (E, G–H): Initial Study Treatment

AE = adverse event; ALP = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CR = completed response; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FACS = fluorescent-activated cell sorting; FLL = follicular lymphoma; GGT = γ-glutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactase dehydrogenase; MRI = magnetic resonance imaging; NALT = new anti-lymphoma treatment; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography; PT = prothrombin time; SAE = serious adverse event; (x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle—refer to footnote 'n' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 6 months (8 cycles on an every-21-day schedule) and may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycle 1 must occur within ±1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 2 should occur within ±2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DCDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 6 months of total study treatment (6 cycles on an every-28-day schedule).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding obinutuzumab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] Cycle 4 Day 15 assessment should be performed between Cycle 4 Day 15 and Cycle 5 Day 1. The Treatment Completion/Early Termination Visit should be performed within 30 days after the last infusion of DCDS4501A or obinutuzumab. The visit at which response assessment shows progressive disease may be used as the early termination visit.

[d] Patients will be followed for safety for 30 days after the last infusions of DCDS4501A or obinutuzumab. Such follow-up will require an assessment (per verbal report from the patient, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 2 years after the last infusions of DCDS4501A or obinutuzumab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-5 for schedule of assessments during the post-treatment period. Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

[e] Informed consent form(s) must be signed by the patient before any study-specific procedures are performed.

[f] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2of the protocol.

[g] Complete physical examination includes all systems described in Section 4.5.1.3.

[h] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDS4501A dosing on Day 2 of each cycle if given on separate days from obinutuzumab only if clinically indicated (e.g., to follow up on signs or symptoms observed from the examinations performed on Day 1).

[i] After informed consent is obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs and SAEs, regardless of attribution, must be reported until 30 days following the last administration of study drug or until the patient receives another anti-cancer therapy, whichever occurs first. After this period, investigators should report only SAEs considered related to prior study treatment *with the exception of second malignancies. Second malignancies will be recorded indefinitely (even if the study has ended) and irrespective of NALT.*

[j] Twelve-lead digital electrocardiogram (ECG) measurements must be obtained in triplicate (with immediately consecutive ECGs obtained until three evaluable ECGs are recorded) at the timepoints specified in Section 4.5.1.5. Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction. The evaluating physician should determine the clinical significance of any abnormal ECGs.

Appendix A-3 (cont.)
Study Flowchart for Obinutuzumab-Containing Cohorts (E, G–H): Initial Study Treatment

[k] Response assessment should be performed using Lugano Response Criteria (Appendix C-2). For patients with DLBCL or FL, a combined PET/CT scan is required during screening, between Cycle 4 Day 15 and Cycle 5 Day 1, EOT assessment, and as clinically indicated. The EOT assessment should be performed 6–8 weeks after Cycle 8 Day 1 or last study treatment. During the follow-up period, scans (CT or PET/CT) should be performed every 6 months for 2 years or until study end or at any time that progression is suspected. Refer to Appendix A-5 for imaging assessment during post-treatment follow-up. Refer to Section 4.5.1.8 for complete details for radiographic assessments.

[l] Administer DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related adverse events. For Cycle 1, DCDS4501A should be administered on the day after obinutuzumab is administered (e.g., Day 2 if obinutuzumab is given on Day 1, or Day 3 if obinutuzumab is given as a split dose on Days 1 and 2). In the absence of any infusion-related adverse events, obinutuzumab followed by DCDS4501A may be administered on the same day in each cycle starting with Cycle 2. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[m] HBsAg, HBcAb, and Hep C Ab serology required. If HBcAb or HCV antibody is positive, HBV/HCV DNA by PCR is required.

[n] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[o] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid., amylase, and lipase Serum GGT levels will be required at screening only.

[p] A serum pregnancy test should be performed for women of childbearing potential within 14 days prior to receiving first study treatment. In addition, a urine pregnancy test must also be performed within 10 days prior to Day 1 of Cycles 3, and 6 and at the treatment completion/early termination visit. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[q] Bone marrow biopsy for morphology (aspirates for morphology and/or flow studies are optional) is required at screening for follicular NHL patients only and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated. Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.

[r] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[s] Availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, obtained at any time prior to entry to study.

[t] All patients who have successfully passed screening and are fully eligible for the study will have a 10-mL plasma sample taken for exploratory research prior to receiving study treatment.

[u] Pharmacokinetic serum and plasma samples and pharmacodynamics blood samples should be drawn according to the schedule provided in Appendix B-3.

[v] Whole blood samples for assessment of anti-DCDS4501A or anti-obinutuzumab antibodies in serum will be drawn according to the schedule provided in Appendix B-3.

Appendix A-4
Study Flowchart: Post-Treatment Follow-Up for Rituximab-Containing Regimens (Arms A-B, Cohorts C–D)

Assessments/Procedures	Post-treatment Follow-up				
Months after treatment completion visit	2 Months	4 Months	6 Months	9 Months	12 Months
Targeted physical examination [a]	x	x	x	x	x
Vital signs (blood pressure, pulse rate, and body temperature)	x	x	x	x	x
ECOG Performance Status	x	x	x	x	x
B symptoms [b]	x	x	x	x	x
Tumor assessments [c]	x	x	x	x	x
Total IgA, IgG, IgM	x	x	x	x	x
Hematology [d]	x	x	x	x	x
Serum chemistry [e]	x	x	x	x	x
Bone marrow [f]	Perform to confirm CR if positive for disease at screening or if clinically indicated				
Central Lab Assessments					
Leukocyte immunophenotyping (FACS) [g]	x	x	x	x	x
Pharmacokinetic sampling [h]	x	x	x		
Serum sample for anti-DCDT2980S / anti-DCDS4501A ATA assay [h]	x	x	x		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATA = anti-therapeutic antibody; CR = completed response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; Ig = immunoglobulin; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography.

Appendix A-4 (cont.)
Study Flowchart: Post-Treatment Follow-Up for Rituximab-Containing Regimens (Arms A-B, Cohorts C–D)

NOTE: Post-treatment assessments apply to patients who discontinue from study treatment (initial or crossover treatment) for reasons other than disease progression. The schedule corresponds to visits timed from treatment completion/early termination visit or crossover treatment completion/early termination visit until the time of disease progression, start of new anti-cancer therapy, or withdrawal from study participation. Two-month and 4-month follow-up visits should occur within ±7 days from the scheduled date, while subsequent visits should occur within ±14 days from the scheduled date.

[a] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms.

[b] Defined as unexplained weight loss >10% over previous 6 months, fever (>38°C/100.4°F), and/or drenching night sweats.

[c] Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C).

[d] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[e] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), and uric acid.

[f] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[g] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[h] Refer to Appendix B1 or B-2.

Appendix A-5
Study Flowchart: Post-Treatment Follow-Up for Obinutuzumab-Containing Regimens (Cohorts E, G-H)

Assessments/Procedures	Post-Treatment Follow-Up					
Months after treatment completion visit	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Targeted physical examination [a]	x	x	x	x	x	x
Vital signs (blood pressure, pulse rate, and body temperature)	x	x	x	x	x	x
ECOG Performance Status	x	x	x	x	x	x
Tumor Assessment (Imaging [PET/CT or C]) [b]		x		x	x	x
Total IgA, IgG, IgM	x	x	x	x	x	x
Hematology [c]	x	x	x	x	x	x
Serum chemistry [d]	x	x	x	x	x	x
Bone marrow [e]	Perform to confirm CR if positive for disease at screening or if clinically indicated					
Central Lab Assessments						
Leukocyte immunophenotyping (FACS) [f]	x	x	x	x	x	x
Pharmacokinetic sampling [g]	x	x		x	x	x
Serum sample for anti-DCDT2980S/anti-DCDS4501A, anti-obinutuzumab ATA assay [g]	x	x		x [g]	x [g]	x [g]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATA = anti-therapeutic antibody; CR = completed response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; Ig = immunoglobulin; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography.

Appendix A-5 (cont.)
Study Flowchart: Post-Treatment Follow-Up for Obinutuzumab-Containing Regimens (Cohorts E, G-H)

NOTE: Post-treatment assessments apply to patients who discontinue from study treatment (initial or crossover treatment) for reasons other than disease progression. The schedule corresponds to visits timed from treatment completion/early termination visit or crossover treatment completion/early termination visit until the time of disease progression, start of new anti-cancer therapy, or withdrawal from study participation. *Three*-month and *6*-month follow-up visits should occur within ±7 days from the scheduled date, while subsequent visits should occur within ±14 days from the scheduled date.

[a] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms.

[b] Response should be assessed using Lugano Response Criteria (Appendix C-2). CT or combined PET/CT scan should be obtained during the post-treatment follow-up up every 6 months for 2 years or until study end or at any time that progression is suspected.

[c] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[d] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid.

[e] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[f] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[g] Refer to Appendix B-3.

Appendix B-1
Serum and Plasma Pharmacokinetic Schedule for DCDT2980S/DCDS4501A and Rituximab, and ATA Schedule for DCDT2980S/DCDS4501A (For Patients Receiving Rituximab on Day 1 and DCDT2980S/DCDS4501A on Day 2 of Every Cycle) (Arms A-B, Cohorts C-D)

Study Visit	Sample Timepoint(s) [a]	Samples [b]
Cycle 1, Day 1	Pre-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycle 1, Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • DCDT2980S/DCDS4501A PK [b]
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 1, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 1, Day 15 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycles 2–3, Day 1	Pre-rituximab dose	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycles 2–3, Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 3, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 3, Day 15 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycles 4, and every 4th cycle thereafter), Day 1	Pre-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycles 4, and every 4th cycle thereafter), Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (± 15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK

Appendix B-1 (cont.)
Serum and Plasma Pharmacokinetic Schedule for DCDT2980S/DCDS4501A and Rituximab, and ATA Schedule for DCDT2980S/DCDS4501A (For Patients Receiving Rituximab on Day 1 and DCDT2980S/DCDS4501A on Day 2 of Every Cycle) (Arms A-B, Cohorts C-D)

Study Visit	Sample Timepoint(s) [a]	Samples [b]
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK [e]
Post-treatment Follow-Up Visits [d]	2, 4, and 6 months after treatment completion visit	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Note: "Pre-infusion" means prior to the start of infusion; "Post-infusion" means after the infusion is completed.

[a] A 3-mL whole-blood sample will be taken for each of the following at each specified timepoint: anti-DCDT2980S or anti-DCDS4501A antibody; rituximab PK; and/or DCDT2980S/DCDS4501A PK. If rituximab dosing is split over two days, then PK will be obtained prior to the rituximab dose on the first day and 30 minutes (±15 minutes) post-rituximab infusion on the second day.

[b] PK sampling will not be obtained from patients who cross-over to another treatment arm.

[c] Cycles 2 and 4 only for anti-DCDT2980S or anti-DCDS4501A antibody.

[d] Post-treatment follow-up PK and ATA assessments only apply to patients who did not receive crossover treatment.

[e] DCDT2980S/DCDS4501A PK including serum PK samples for total DCDT2980S and DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

Appendix B-2
Serum and Plasma Pharmacokinetic Schedule for Rituximab and DCDT2980S/DCDS4501A, and ATA Schedule for DCDT2980S/DCDS4501A for Patients Receiving Rituximab and DCDT29808S/DCDS4501A on Day 1 of Every Cycle Beginning Cycle 3 (Arms A-B, Cohorts C-D)

Study Visit	Sample Timepoint(s) [a]	Samples [b]
For Cycle 1 and Cycle 2 PK assessments, refer to Appendix B-1		
Cycle 3, Day 1	Pre-rituximab infusion	• Rituximab PK • DCDT2980S/DCDS4501A PK [e]
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 3, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 3, Day 15 (±1 day)		• Rituximab • DCDT2980S/DCDS4501A PK
Cycles 4, and every 4th cycle thereafter), Day 1	Pre-rituximab infusion	• Rituximab PK • Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK
Post-treatment Follow-Up Visits [d]	2, 4, and 6 months after treatment completion visit	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK

Appendix B–2 (cont.)
Serum and Plasma Pharmacokinetic Schedule for Rituximab and DCDT2980S/DCDS4501A, and ATA Schedule for DCDT2980S/DCDS4501A for Patients Receiving Rituximab and DCDT29808S/DCDS4501A on Day 1 of Every Cycle Beginning Cycle 3 (Arms A-B, Cohorts C-D)

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Note: "Pre-infusion" means prior to the start of infusion; "Post-infusion" means after the infusion is completed.

[a] A 3-mL whole-blood sample will be taken for each of the following at each specified timepoint: anti-DCDT2980S or anti-DCDS4501A antibody, rituximab PK, and/or DCDT2980S/DCDS4501A PK. If rituximab dosing is split over two days, then PK will be obtained prior to the rituximab dose on the first day and 30 minutes (± 15 minutes) post-rituximab infusion on the second day.

[b] PK sampling will not be obtained from patients who cross-over to another treatment arm.

[c] Cycles 4 only for anti-DCDT2980S or anti-DCDS4501A antibody.

[d] Post-treatment follow-up PK and ATA assessments only apply to patients who did not receive crossover treatment.

[e] DCDT2980S/DCDS4501A PK including serum PK samples for total DCDT2980S and DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

Appendix B–3
Serum and Plasma Pharmacokinetic, Blood Pharmacodynamic, and ATA Schedule for Obinutuzumab and DCDS4501A (Cohorts E, G–H)

Study Visit	Sample Timepoint(s) [a]	Samples [a]
Cycle 1, Day 1	Pre-obinutuzumab infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • PD Blood [c]
	End of obinutuzumab infusion	• Obinutuzumab PK (serum) • PD Blood [c]
Cycle 1, Day 2	Pre-DCDS4501A infusion	• DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
	End of DCDS4501A infusion	• DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
Cycle 1, Day 8	6 days (±1 day) after Day 2 infusion	• DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
Cycle 1, Day 15	13 days (±1 day) after Day 2 infusion	• DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
Cycle 2, Day 1	Pre-obinutuzumab infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • PD Blood [c]
	End of obinutuzumab infusion	• PD Blood[c]
	Pre-DCDS4501A infusion	• DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
	End of DCDS4501A infusion	• PD Blood
Cycle 4, Day 1	Pre-obinutuzumab infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum)
	End of obinutuzumab infusion	• Obinutuzumab PK (serum)
	Pre-DCDS4501A infusion	• DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b]
	End of DCDS4501A infusion	• DCDS4501A PK (serum and plasma)[b]
Cycle 4 Day 15	Aligned with PET imaging	• PD Blood [c]
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b]
End of Treatment Assessment Visit	6–8 weeks after last study dose	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b]

Appendix B–3 (cont.)
Serum and Plasma Pharmacokinetic and ATA Schedule for Obinutuzumab and DCDS4501A (Cohorts E, G-H)

Study Visit	Sample Timepoint(s) [a]	Samples [a]
		• PD Blood [c]
Post-treatment Follow-Up Visits	3 and 6 months after treatment completion visit	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
	9 months after treatment completion visit	• PD Blood [c]
	12 and 18 months after treatment completion visit	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • PD Blood [c]
	24 months after treatment completion visit	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • PD Blood [c]

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Note: "Pre-infusion" means prior to the start of infusion; "End-of-infusion" samples should be drawn 30 minutes (±15 minutes) unless otherwise specified.

[a] Up to 10-mL whole-blood samples will be taken for obinutuzumab PK, obinutuzumab ATA, obinutuzumab concentration, DCDS4501A PK (DCDS4501A total antibody, unconjugated MMAE and conjugate [evaluated as antibody-conjugated MMAE]), DCDS4501A ATA, DCDS4501A concentration, and for exploratory studies at each specified point with separate tubes for plasma or serum samples. If obinutuzumab dosing is split over two days, then PK will be obtained prior to the obinutuzumab dose on the first day and 30 minutes (±15 minutes) post-obinutuzumab infusion on the second day.

[b] DCDS4501A PK including serum PK samples for total DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

[c] Up to 10-mL whole-blood samples will be taken for exploratory studies at each specified timepoint with separate tubes.

Appendix C-1
Modified Response and Progression Criteria for NHL

Adapted from: Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol 2007;25:579–86.

Selection of Indicator (Target) Lesions

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions

  Abnormal lymph nodes are those that are either

  > 15 mm in the greatest transverse diameter (GTD) regardless of the short axis diameter, or

  > 10 mm in short axis diameter regardless of long axis

- If possible, they should be from disparate regions of the body.
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

PET Scans--Definition of a Positive PET scan

Visual assessment currently is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary. In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff. Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen uptake, and diffusely increased bone marrow uptake within weeks after treatment.

Complete Remission (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy.

   Typically FDG-avid lymphoma: in patients with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, the designation of CR requires all nodal indicator lesions to regress to the size of normal lymph nodes. Lymph nodes that were >15 mm in GTD regardless of the short axis diameter at the screening tumor assessment must regress to ≤ 15 mm in GTD regardless of the short axis diameter. Lymph nodes that were 11 to 15 mm in GTD and >10 mm in the short axis diameter at the screening tumor assessment must regress to ≤ 10 mm in the short axis diameter.

2. The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

3. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (>20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial Remission (PR)

1. $\geq 50\%$ decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; (b) if possible they should be from disparate regions of the body; (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by $\geq 50\%$ in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

Appendix C–1 (cont.)
Modified Response and Progression Criteria for NHL

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
6. No new sites of disease should be observed (e.g., nodes $>$ 1.5 cm in any axis).
7. *Typically FDG-avid lymphoma*: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. *Variably FDG-avid lymphomas/FDG-avidity unknown*: for patients without a pretreatment PET/CT scan, or if a pretreatment PET/CT scan was negative, CT criteria should be used.
9. In patients with follicular lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease (SD)

1. Failing to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease (see below).
2. *Typically FDG-avid lymphomas*: the PET should be positive at prior sites of disease with no new areas of involvement on the post- treatment CT or PET.
3. *Variably FDG-avid lymphomas/FDG-avidity unknown*: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (RD; after CR) or Progressive Disease (PD; for Patients with PR or SD)

1. Lymph nodes should be considered abnormal if the long axis is $>$ 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1–1.5 cm, it should only be considered abnormal if its short axis is $>$ 1.0. Lymph nodes $\leq$ 1.0 cm by $\leq$ 1.0 cm will not be considered as abnormal for relapse or progressive disease.
2. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities.

Appendix C–1 (cont.)
Modified Response and Progression Criteria for NHL

3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or more than 1.5 cm in the long axis.
4. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
5. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 15 mm in its long axis by CT).
6. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease.

Appendix C–2
Revised Criteria for Response Assessment: The Lugano Classification (Cohorts E, G–H)

Response should be determined on the basis of radiographic and clinical evidence of disease. For the end-of-treatment response assessment, an ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET)/computed tomography (CT) scan will be performed 6–8 weeks after Cycle 8 Day 1 or last study treatment as assessed by the Independent Review Committee and by the investigator. Assessment of PET/CT scan should follow the criteria described by Cheson (2014) presented below.

Selection of measured dominant (indicator) lesions:

- Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected should be clearly measurable in two diameters:

  A measurable node must have a longest transverse diameter of a lesion (LDi) $>$1.5 cm.

  A measurable extranodal lesion should have an LDi $>$1.0 cm.
- Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.
- Non-nodal lesions should include those in solid organs (e.g., liver, spleen, kidneys, and lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation.
- If possible, they should be from disparate regions of the body.
- They should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

Selection of non-measured (non-indicator) lesions:

- Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured.

  These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

Appendix C–2 (cont.)
Revised Criteria for Response Assessment: The Lugano Classification (Cohorts E, G-H)

In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, and bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but it should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

Response	Site	PET/CT–Based Response	CT-Based Response
Complete		**Complete metabolic response**	**Complete radiologic response (all of the following)**
	Lymph nodes and extralymphatic sites	• Score 1, 2, or 3 [a] with or without a residual mass on 5-PS [b] • It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	• Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi • No extralymphatic sites of disease
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	• No evidence of FDG-avid disease in marrow • *Normal by morphology, if indeterminate, IHC negative*	Normal by morphology; if indeterminate, IHC negative

Appendix C–2 (cont.)
Revised Criteria for Response Assessment: The Lugano Classification (Cohorts E, G-H)

Response	Site	PET/CT–Based Response	CT-Based Response
Partial		**Partial metabolic response**	**Partial remission (all of the following)**
	Lymph nodes and extralymphatic sites	• Score of 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease. • At end of treatment, these findings indicate residual disease.	• ≥50% decrease in SPD of up to 6 target measureable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value • When no longer visible, 0 × 0 mm • For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or stable disease		**No metabolic response**	**Stable disease**
	Target nodes/nodal masses, extranodal lesions	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD for up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Nonmeasured lesions	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable

Appendix C–2 (cont.)
Revised Criteria for Response Assessment: The Lugano Classification (Cohorts E, G-H)

Response	Site	PET/CT–Based Response	CT-Based Response
Progressive disease		**Progressive metabolic disease**	**Progressive disease (requires at least one of the following)**
	Individual target nodes/nodal lesions and extranodal lesions	• Score 4 or 5 [b] with an increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: • LDi > 1.5 cm AND • Increase by ≥ 50% from PPD nadir AND An increase in LDi or SDi from nadir • 0.5 cm for lesions ≤ 2 cm • 1.0 cm for lesions > 2 cm
	Nonmeasured lesions	None	New or clear progression of preexisting *nonmeasured lesions*
	Organ enlargement		• In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. • New or recurrent splenomegaly
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	• Regrowth of previously resolved lesions A new node > 1.5 cm in any axis • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-acid foci	New or recurrent involvement

Appendix C–2 (cont.)
Revised Criteria for Response Assessment: The Lugano Classification (Cohorts E, G-H)

5-PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment).

[b] PET 5-PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake < mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

REFERENCE

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059–68.

Appendix D
Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Appropriate monitors (electrocardiogram, blood pressure, pulse oximetry
- Oxygen
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines.
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional assistance!
- Maintain an adequate airway.
- Provide oxygen as needed.
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible.
- Administer antihistamines, epinephrine, inhaled bronchodilators, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix E
M. D. Anderson Symptom Inventory (MDASI)

M.D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24*** hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (symptom is as bad as you can imagine it could be) for each item.

	Not Present										**As Bad As You Can Imagine**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problems **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problems with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your **mouth/throat sores** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **diarrhea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your problems with **weakness in the arms or legs** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Appendix E (cont.)
M. D. Anderson Symptom Inventory (MDASI)

Part II. How have your symptoms interfered with your life?
Symptoms frequently interfere with how you feel and function. How much have your symptoms interfered with the following items **in the last 24** hours:

	Did Not Interfere										**Interfered Completely**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
18. General activity?	○	○	○	○	○	○	○	○	○	○	○
19. Mood?	○	○	○	○	○	○	○	○	○	○	○
20. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
21. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
22. Walking?	○	○	○	○	○	○	○	○	○	○	○
23. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

Appendix F
Recommendations for the Use of White Blood Cell Growth Factors

Primary Prophylactic G-CSF Administration (First and Subsequent-Cycle Use)

Primary prophylaxis with G-CSF is recommended if any of the following clinical factors are present:

- Age >65 years
- Poor performance status
- Previous history of febrile neutropenia
- Open wounds or active infections
- More advanced cancer
- Extensive prior treatment, including large radiation therapy ports
- Cytopenias due to bone marrow involvement by tumor
- Other serious comorbidities

Secondary Prophylactic G-CSF Administration

Prophylactic G-CSF administration is recommended for patients who fulfill each of the following circumstances:

- Experienced a neutropenic complication from a prior cycle of study treatment
- Primary prophylactic G-CSF was not received; and
- The intent is to avoid dose reduction of the antibody–drug conjugate (ADC), where the effect of the reduced dose on disease-free, overall survival or treatment outcome is not known

Therapeutic Use of G-CSF

G-CSF administration should be considered for the following patients:

- Patients with febrile neutropenia who are at high risk for infection-associated complications; or
- Patients who have prognostic factors that are predictive of poor clinical outcome, e.g., prolonged (>10 days) and profound (<100/μL) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of fever development

Source: Smith TJ et al. 2006 Update of Recommendations for the use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. JCO 24:3187-3205. 2006.

PROTOCOL

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF PINATUZUMAB VEDOTIN (DCDT2980S) IN COMBINATION WITH RITUXIMAB OR POLATUZUMAB VEDOTIN (DCDS4501A) IN COMBINATION WITH RITUXIMAB AND A NON-RANDOMIZED PHASE IB/II EVALUATION OF POLATUZUMAB VEDOTIN IN COMBINATION WITH OBINUTUZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
EUDRACT NUMBER:	2011-004377-84
STUDY DRUG:	Pinatuzumab Vedotin (DCDT2980S); Polatuzumab Vedotin (DCDS4501A)
IND:	107713
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	27 July 2012
DATE AMENDED:	Version A1: 24 June 2013 Version A2: *6 November 2014.* *Version A3: See electronic date stamp below.*

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Clinical Science Leader	30-Apr-2015 15:38:20

PROTOCOL AMENDMENT, VERSION A*3*: RATIONALE

Protocol GO27834 has been amended to enable the following changes:

- In addition to sites in the United States, sites worldwide will now participate in the enrollment of patients into the non-randomized expansion cohorts (G and H) of the obinutuzumab portion of the study. Cohorts G and H will each contain 40 patients with a diagnosis of either follicular NHL (Cohort G) or DLBCL (Cohort H) and will receive DCDS4501A at 1.8mg/kg in combination with obinutuzumab.
- In Section 1.2.3, the reference for Rituximab was updated from Product Insert/Summary of Product Characteristics to Investigator's Brochure because Rituximab is an IMP in the protocol.
- The criteria for opening enrollment to the expansion portion of the study have been modified. Six patients will complete the safety observation period in the safety run-in phase of the study before the expansion portion of the study can begin, because sufficient safety data will be collected to determine whether the 1.8 mg/kg dose of DCDS4501A (polatuzumab vedotin) is safe in combination with obinutuzumab.
- Guidelines for dose modification of DCDS4501A (polatuzumab vedotin) have been updated to allow for dose reductions to 1.4 mg/kg of polatuzumab vedotin for Grade 2 or Grade 3 peripheral neuropathy. Dose reductions below 1.8 mg/kg of polatuzumab vedotin for neutropenia will not be allowed.
- ePRO MDASI assessments have been removed for the obinutuzumab cohorts, as no comparison will be made for ePRO between the obinutuzumab and rituximab cohorts. Only the rituximab cohorts will be assessed for ePRO.
- Non-serious adverse events of special interest for this study have been updated as described below. The proposed update does not impact the routine collection and regulatory reporting of the adverse events that are removed from the AESI list.

  Peripheral neuropathy (sensory and/or motor) is already classified as an adverse drug reaction for polatuzumab vedotin. Therefore, non-serious adverse events suggestive of the diagnosis or signs/symptoms of peripheral neuropathy no longer need to be reported immediately by the investigator to the Sponsor. This administrative amendment does not change the Sponsor's approach in close monitoring of data suggestive of peripheral neuropathy. Comprehensive adverse event documentation of actions taken on occurrence of the diagnosis or signs/symptoms suggestive of sensory and/or motor neuropathy and the adverse event outcome will continue.

  In addition, revision was made to include tumor lysis syndrome, a program-wide AESI for obinutuzumab.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION A*3*:
SUMMARY OF CHANGES

COVER PAGE

The Medical Monitor has been changed from [redacted]*, M.D. to* [redacted] *M.D.*

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2.3: Rituximab

Refer to the Rituximab ~~Product Insert/Summary of Product Characteristics~~ *Investigator's Brochure* for complete details regarding clinical data related to approved indications.

SECTION 1.3.1: Rationale for Assessing ADC Dose of 1.8 mg/kg Combined with Rituximab in iNHL

In contrast to iNHL, treatment paradigms in relapsed or refractory aggressive lymphomas such as DLBCL continue to place a premium on anti-tumor activity and higher tolerance for treatment-related toxicity, given that *the* duration~~s~~ of disease control and survival are substantially shorter and that treatment options are extremely limited. Early Phase I data suggest lower rates of study treatment discontinuation for adverse events among patients with DLBCL compared with patients with iNHL. Taken together with anti-tumor activity observed to date, the benefit-risk profile of the currently tested ADC dose of *1.8*~~2.4~~ mg/kg is considered acceptable *to combine with rituxminab in the treatment of patients with iNHL.*

SECTION 2.1: PRIMARY OBJECTIVES

- To assess the anti-tumor activity of the combination of DCDS4501A and obinutuzumab in patients with relapsed or refractory follicular NHL and DLBCL *based on PET-CR at the end of treatment according to IRC per Lugano 2014 response criteria*

SECTION 2.2.2: Activity Objectives

The secondary activity objective *for rituximab-containing arms* of the study is the following:

- To compare the anti-tumor activity of the combination of DCT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab

The secondary activity objectives for obinutuzumab-containing arms of the study are the following:

- *CR at end of treatment based on PET alone, as determined by the investigator*
- *Objective response (OR; CR or PR) at end of treatment based on PET alone as determined by investigator and IRC*
- *CR at end of treatment based on CT only as determined by the investigator and IRC*
- *OR at end of treatment based on CT only as determined by the investigator and IRC*

- *Best objective response (BOR, CR or PR) while on study based on PET alone or CT only, as determined by the investigator*

SECTION 2.3.1: *Efficacy Objectives*

The exploratory efficacy objectives for this study are to evaluate the long-term outcome of obinutuzumab-treated patients according to Lugano 2014 response criteria, as measured by the following:

- *Duration of response based on PET and/or CT scans*
- *Progression-free survival (PFS) based on PET and/or CT scans*
- *Event-free survival (EFS) based on PET and/or CT scans*
- *Overall survival*

SECTION 2.3.3: Patient-Reported Outcomes Objective

- To assess patient-reported tolerability to study treatment and the impact of study treatment on patient functioning on the basis of PRO *in Rituximab cohorts only*

SECTION 3.1: DESCRIPTION OF THE STUDY

This is a Phase Ib/II, multicenter, open-label study. Up to approximately 2*46*~~52~~ patients with relapsed or refractory FL and DLBCL will be enrolled at approximately 30–40 investigative sites worldwide.

Only investigational sites in the United States will enroll patients into Cohort E. Investigational sites in the United States~~, and Canada~~ *and worldwide* will participate in Cohorts G and H~~)~~.

SECTION 3.1.1.1: Randomized Portion of the Study (Arms A and B) – *Closed to Enrollment*

SECTION 3.1.1.2: Randomized Portion of the Study with Rituximab (Cohorts C and D) – *Closed to Enrollment*

SECTION 3.1.3.1: Obinutuzumab-Containing Regiment in Phase Ib: Safety Run-In (Cohort E)

This portion of the study will consist of a safety run-in that will evaluate the safety of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in 6 patients (Cohort E). The safety run-in is described in detail in Section 3.4. ~~In case an amendment to the protocol allows to study higher doses of DCDS4501A, the safety run in for the 1.8 mg/kg may be shortened to 3 patients.~~

SECTION 3.2: RATIONALE FOR STUDY DESIGN

DCDT2980S and DCDS4501A ~~are~~*were* both ~~being~~ evaluated as single agents and in combination with rituximab in the ~~ongoing~~ Phase I studies Study DCT4862g and Study DCS4968g, respectively.

Study GO27834 will continue to assess the cumulative safety and longer-term tolerability of ADC-rituximab combination therapy. *Due to additional information about the benefit-risk profile of DCDS4501A at the 2.4 mg/kg dose, the Sponsor is no longer pursuing the 2.4 mg/kg dose of DCDS4501A in the obinutuzumab-containing cohorts.*

SECTION 3.3.3: Activity Outcome Measures

The following activity outcome measures will be assessed *for rituximab-containing arms/cohorts (Arms A and B, Cohort C)*:

The following activity outcome measures will be assessed for obinutuzumab-containing cohorts (Cohorts E, G, and H) according to Lugano 2014 Response Criteria (Cheson et al. 2014):

The primary activity outcome measure will be assessed by:

- *CR at end of treatment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) based on PET alone, as determined by the IRC*

The following secondary efficacy outcome measures will be assessed:

- *OR (CR or PR) at end of treatment based on PET alone as determined by the investigator and IRC*
- *CR at end of treatment based on CT only, as determined by the investigator and IRC*
- *OR (CR or PR) at end of treatment based on CT only as determined by the investigator and IRC*
- *BOR (CR or PR) while on study based on PET alone or CT only, as determined by the investigator*

SECTION 3.3.4: Exploratory Outcome Measures

- Treatment and disease symptom assessments using the M.D. Anderson Symptom Inventory (MDASI) *in rituximab-containing cohorts only*

The following exploratory efficacy outcome measures will be assessed:

- *DOR, defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse, or death from any cause, for the subgroup of patients with a best overall response of CR or PR, based on PET and/or CT scans as determined by the investigator assessment. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the DOR will be censored on the date of last disease assessment.*
- *PFS, defined as the time from date of randomization or first treatment (for G-containing arms) to the first occurrence of progression or relapse, or death from any cause , based on PET and/or CT scans as determined by the investigator assessment.*
- *EFS, defined as the time from date of randomization or first treatment (for G-containing arms) to any treatment failure including disease progression relapse, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first, based on PET and/or CT scans as determined by the investigator assessment*
- *OS, defined as the time from the date of first treatment to the date of death from any cause*

SECTION 3.4.1: Safety Run-In Analysis

As outlined in Figure 3b and Section 3.1.3.1, a safety run-in analysis (Cohort E) will be conducted by the Internal Monitoring Committee (IMC) to evaluate the combination of DCDS4501A at a dose of 1.8 mg/kg with obinutuzumab. This analysis will include data from the first 6 patients treated through *the safety observation period, from Cycle 1 Day 1 to* ~~Day 21 of Cycle 1~~*Cycle 2 Day 1 for a minimum of 21days*. Three patients will initially be enrolled, and then an additional 3 patients will be enrolled after the first 3 patients have safely completed the first cycle. *The decision to enroll an additional 3 patients will be made by the Sponsor's Medical Monitor in consultation with the safety science leader, biostatistician, and participating investigators.* At the IMC's discretion, and at any point during enrollment of the safety run-in, a decision could be made that more than 6 patients are needed to evaluate safety. *Additional patients may also be enrolled at dose levels below 1.8 mg/kg of DCDS4501A (i.e., 1.4 mg/kg) based upon review of all safety data.* ~~In this case, the protocol will be amended to allow for more than 6 patients in the safety run in. In case the study is amended to test additional doses the safety run in for 1.8 mg/kg may be shortened to three patients.~~

Before the expansion portion of the study can begin (enrollment of Cohorts G and H), ~~the following criteria must be met:~~

s~~S~~ix patients must have completed ~~enrollment~~ *the safety observation period (Cycle 1 Day 1 to Cycle 2 Day 1 for a minimum of 21 days)* in the safety run-in (Cohort E).

~~1. Three patients must have completed at least 4 cycles of treatment.~~

SECTION 3.4.2: Internal Monitoring Committee

The IMC will include *the Roche/Genentech Medical Monitor, at least one other Clinical Science representative who is not directly involved in the study*,~~a sponsor Medical Monitor not affiliated with the study~~, a Drug Safety Scientist, a biostatistician, and a statistical programmer.

Throughout the course of the study, the IMC will meet~~,~~ *at regular intervals during the study and* ~~as needed,~~ at the request of the Medical Monitor (e.g., on the basis of unexpected safety signals).

Specific operational details such as the committee's composition, frequency and timing of meetings and members' roles and responsibilities will be detailed ~~Complete details of the IMC will be described~~ in the IMC charter.

SECTION 3.4.5.7: Immunization

The safety of immunization with live viral vaccines following rituximab therapy has not been studied. Patients who participate in this study may not receive either primary or booster ~~vaccination~~ with live virus vaccines for at least *28 days* ~~6 months~~ prior to initiation of rituximab or at any time during study treatment. Investigators should review the

~~vaccination~~ status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult ~~vaccination~~ with non-live vaccines intended to prevent infectious diseases prior to study therapy.

SECTION 3.4.6.2: Tumor Lysis Syndrome

TLS has been reported with obinutuzumab administration. Patients with a high tumor burden, including patients with a lymphocyte count $\geq 25 \times 10^9$/L, particularly patients with B-cell CLL and MCL, are at increased risk for TLS and severe IRRs. All patients with peripheral blood lymphocyte counts of $\geq 25 \times 10^9$/L or bulky adenopathy must receive prophylaxis for TLS prior to the initiation of study treatment. This includes appropriate hydration, consisting of fluid intake of approximately 3 L/day, starting 1–2 days prior to the first dose of obinutuzumab, and administration of allopurinol (300 mg/day orally) or a suitable alternative (i.e., rasburicase) treatment, starting at least *12 –24*~~72~~ hours prior to the first infusion of obinutuzumab (Cycle 1, Day 1). All patients should then be carefully monitored during the initial weeks of treatment. Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts $\geq 25 \times 10^9$/L) before the second and subsequent infusions of obinutuzumab should receive continuous TLS prophylaxis with allopurinol or a suitable alternative (i.e., rasburicase) and adequate hydration until the risk is abated, as determined by the investigator. *For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.*

SECTION *3.4.6.6*: *Immunization*

The safety of immunization with live virus vaccines following obinutuzumab therapy has not been studied. Thus, vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

SECTION *3.4.6.7*: *Worsening of Preexisting Cardiac Condition*

In patients with underlying cardiac disease and treated with obinutuzumab, adverse events such as angina pectoris, acute coronary syndrome, myocardial infarction, heart failure, and arrhythmias, including atrial fibrillation and tachyarrhythmia, have been observed. These events may occur as part of an IRR and can be fatal. Therefore, patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution to prevent a potential fluid overload.

SECTION 4.1.2: <u>Exclusion Criteria</u>

- *Vaccination with a live vaccine within 28 days prior to treatment*

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT

For obinutuzumab-containing cohorts (Cohorts E, G, and H), patients with either relapsed or refractory follicular NHL or relapsed or refractory DLBCL will be enrolled. After the safety run-in stage for DCDS4501A at 1.8 mg/kg in combination with obinutuzumab, the *non-randomized dose-expansion portion of the study will enroll 40 relapsed or refractory FL* patients *into Cohort G and 40 relapsed or refractory DLBCL*

patients into Cohort H. ~~will be enrolled into the dose expansion portion with 40 patients in each histology group.~~

SECTION 4.3.1.2: Dosage and Administration

c. **General Information**

The total dose of DCDT2980S and DCDS4501A for each patient will depend on the patient's weight within 96 hours prior to Day 1 of each cycle. The patient weight obtained during screening may be used for dose determination at all treatment cycles; if the patient's weight within 96 hours prior to Day 1 of a given treatment cycle differs by >10% from the weight obtained during screening, ~~then~~ the new weight should be used to calculate the dose.

SECTION 4.3.1.3: Dosage Modification

Specific guidelines around dosage modifications for neutropenia and peripheral neuropathy are detailed below in Sections 4.3.1.6 and 4.3.1.7. Patients who experience other treatment-related Grade 3 or 4 toxicity or laboratory abnormalities will be allowed to delay dosing of study treatment (both ADC and rituximab or obinutuzumab) for up to 2 weeks to allow for recovery. Patients may continue to receive additional infusions of DCDT2980S or DCDS4501A per their treatment assignment provided that the toxicity has resolved to Grade $\leq$2 or $\geq$80% of the baseline value, whichever is lower, within the 2-week delay period. ~~Upon resolution, the dose for subsequent infusions may be reduced to 1.8 mg/kg (in Cohorts C and D). If the toxicity that resulted in the dose reduction persists or recurs at the reduced dose, then the patient should be discontinued from study treatment.~~ The decision for dose modification will be made on the basis of the investigator's assessment of ongoing clinical benefit with continued study treatment and in consultation with the Medical Monitor.

Once dose reductions of DCDT2980S or DCDS4501A are made for toxicity, dose re-escalation will not be allowed. ~~Patients who are enrolled in the non randomized portion of the study (Cohorts C and D), are dosed at an ADC dose of 1.8 mg/kg, and have progressive disease in the absence of any drug related toxicity may have their ADC dose increased to 2.4 mg/kg if it is felt that there is reasonable justification for ongoing clinical benefit. The decision to increase the dose must be made in consultation with and approval of the Medical Monitor. Patients in Cohorts E, G, and H (obinutuzumab-containing cohorts) will not be eligible for dose escalation.~~

SECTION 4.3.1.6: Neutropenia

- If prophylactic G-CSF was not administered prior to the cycle in which the Grade 3–4 neutropenia developed, then prophylactic G-CSF may be administered prior to subsequent cycles without DCDT2980S/DCDS4501A dose reduction. The dose schedule may be changed from 21-day to 28-day cycles to provide sufficient time for neutrophil recovery in subsequent cycles. In the absence of prophylactic G-CSF or dose schedule modification, the dose of DCDT2980S/DCDS4501A in subsequent cycles should be reduced to 1.8 mg/kg *for Arms A and B*. For Cohorts

E, G, and H, patients will be given DCDS4501A at a dose of 1.8 mg/kg, and further dose reductions cannot be made.

- If Grade 3–4 neutropenia recurs with prophylactic G-CSF, the dose for subsequent DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg *for Arms A and B*. Prophylactic G-CSF and dose schedule modifications as described above are permitted in order to maintain the reduced DCDT2980S/DCDS4501A dose level and schedule.
- For patients enrolled into the non-randomized portion of the study (Cohorts C and D, as well as Cohorts E, G, and H), dose *reductions*~~modifications~~ will not be allowed *for neutropenia*. Administration of therapeutic/prophylactic G-CSF and dose-schedule modifications as described above are allowed. Patients who have persistent or recurrent Grade 3–4 neutropenia as defined above should be discontinued from study treatment.

SECTION 4.3.1.7: Peripheral Neuropathy

Peripheral neuropathy (sensory *and/*or motor) is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.2.5). For new or worsening drug-related Grade 2 or 3 peripheral sensory and/or motor neuropathy, dosing should be held for up to 2 weeks until peripheral neuropathy ~~(sensory or motor)~~ improves to Grade 1 or baseline grade. Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and approval of the Medical Monitor based on an assessment of the benefit-risk analysis of continuing to delay study treatment.

For patients enrolled on arms A or B f~~F~~ollowing resolution of peripheral neuropathy (sensory and/or motor), subsequent doses of DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg. ~~DCDS4501A should not be reduced to a dose lower than 1.8 mg/kg.~~ If worsening Grade 2 or 3 **peripheral** neuropathy (sensory and/or motor) recurs following dose reduction, study treatment should be discontinued. For Grade *4*~~3~~ peripheral neuropathy (sensory and/or motor), study treatment should be discontinued.

For patients enrolled into *Cohorts C and D,* ~~the non-randomized portion of the study (Cohorts C and D),~~ dose modifications will not be allowed. Patients who have Grade 2 or 3 peripheral neuropathy (sensory and/or motor), as defined above, should be discontinued from study treatment.

For patients enrolled on Cohorts E, G, or H, following resolution of Grade 2 or Grade 3 peripheral neuropathy (sensory and/or motor), subsequent doses of DCDS4501A should be permanently reduced from 1.8 mg/kg to 1.4 mg/kg. If worsening Grade 2 or Grade 3 peripheral neuropathy (sensory and/or motor) recurs following dose reduction, study treatment should be discontinued. For Grade 4 peripheral neuropathy (sensory and/or motor), study treatment should be discontinued.

SECTION 4.3.3.4: Schedule Modification

Specific guidelines around schedule modifications for thrombocytopenia *and febrile neutropenia* are detailed below in Section 4.3.3.5 *and Section 4.3.3.6*.

SECTION 4.3.3.5: Thrombocytopenia

In the event of severe thrombocytopenia (platelet count $<$10,000/μL) and/or symptomatic bleeding (irrespective of platelet count) in patients who are not receiving concomitant anticoagulants or platelet inhibitors:

- Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves. If *Cycle 1 Day 8 is delayed, then skip Day 8 and administer Day 15 as previously scheduled (if thrombocytopenia or symptomatic bleeding has resolved). If Cycle 1 Day 15 is delayed, then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab and DCDS4501A as scheduled (if thrombocytopenia or symptomatic bleeding has resolved).* ~~but do not skip any doses of obinutuzumab for the sake of maintaining the study treatment schedule.~~

In the event of thrombocytopenia with platelet count $<$20,000/μL and/or symptomatic bleeding (irrespective of platelet count) in patients who are receiving concomitant anticoagulants or platelet inhibitors:

- Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves~~., but do not skip any doses of obinutuzumab for the sake of maintaining the study treatment schedule.~~ *If Cycle 1 Day 8 is delayed, then skip Day 8 and administer Day 15 as previously scheduled (if thrombocytopenia or symptomatic bleeding has resolved). If Cycle 1 Day 15 is delayed, then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab and DCDS4501A as scheduled (if thrombocytopenia or symptomatic bleeding has resolved).*

SECTION *4.3.3.6: Febrile Neutropenia*

In the event of febrile neutropenia or neutropenia with infection, hold obinutuzumab until febrile neutropenia or neutropenia with infection resolves.

- *If Cycle 1 Day 8 is delayed long enough that the patient is approaching Day 15, then skip Day 8 and administer Day 15 as previously scheduled (if infection or fever has resolved)*
- *If Cycle 1 Day 15 is delayed long enough that the patient approaching Cycle 2, then skip Day 15 dosing and administer Cycle 2 Day 1 of DCDS4501 as scheduled (if infection or fever has resolved)*
- *Note: Obinutuzumab* Patients will receive DCDT2980S or DCDS4501A at 1.8 mg/kg or 2.4 mg/kg by IV infusion on Day 1 or Day *should not be held for neutropenia without fever or infection*

SECTION 4.4.1: <u>Concomitant Therapy</u>

For patients enrolled on obinutuzumab-containing regimens, it is recommended that *corticosteroids (e.g., 100 mg of IV prednisolone or equivalent)* ~~oral prednisone, prednisolone, or methylprednisolone~~ be given as premedication within 12 hours of, but at least 60 minutes prior to, the obinutuzumab infusion on Cycle 1 Day 1.

SECTION 4.5.1.4: Laboratory Assessments

Central Laboratory Assesssments

- ATA assays

ATAs to DCDT2980S, DCDS4501A, or obinutuzumab will be determined ~~at Genentech~~ using ~~a~~ validated ELISA*s* (see Section 4.9).

Local Laboratory Assesssments

- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid*, amylase, and lipase*

SECTION 4.5.1.5: Electrocardiogram Assessments

- Day 8 (±1 day) of Cycle 3 time matched (i.e., obtained at the same time of day) with post-DCDT2980s/DCDS4501A infusion ECGs for Cycle 3 ~~only for rituximab-containing arms/cohorts~~

SECTION 4.5.1.8: Tumor Response Assessments

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, on the basis of physical examinations, CT scans, PET scans, and/or MRI scans, and bone marrow examinations, using standard response criteria for NHL (Cheson et al. 2007*; Cheson et al. 2014*) (see Appendix C-1 and C-2).

b. Radiographic Assessments for Patients on Obinutuzumab-Containing Cohorts

PET and CT scans are required for follicular NHL and DLBCL patients at screening, after Cycle 4 of study treatment (i.e., between Cycle 4 Day 15 and Cycle 5 Day 1), and at EOT. The EOT response assessment should be performed 6–8 weeks after Cycle 8 Day 1 or last study treatment. CT scans without PET scans will be obtained every *6*~~3~~ months for *2*~~1~~ year*s*, ~~then every 6 months for 1 year, for a total of approximately 2 years after the treatment completion visit,~~ with use of *Lugano 2014*~~standard~~ *R*~~r~~esponse *C*~~c~~riteria for NHL (see Appendix C-2).

c. Bone Marrow Assessments

A bone marrow biopsy for morphology is required at screening and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. *For obinutuzumab-containing cohorts, only follicular NHL patients are required to undergo a bone marrow biopsy at screening.*

SECTION 4.5.1.10: Patient-Reported Outcomes

PRO data will be elicited from all patients in this study *(with the exception of Cohorts E, G, and H)* to more fully characterize the clinical profile of study treatment. The MDASI PRO instrument will be supplied in the local language of each participating country. Electronic (handheld computers) will be used for the daily collection of symptoms derived from the MDASI.

SECTION 4.5.2: Screening and Pretreatment Assessments

Bone marrow biopsy and aspirate specimens are required at screening (see Section 4.5.1.8). *For obinutuzumab-containing cohorts, bone marrow biopsy and aspirate are only required for follicular NHL patients*. Unsuccessful attempts at obtaining marrow aspirates will not be considered a protocol deviation or violation.

SECTION 4.9.6: Anti-Therapeutic Antibody

ATAs against obinutuzumab in serum samples will be measured using a validated bridging antibody ELISA *and characterized by a competitive binding assay*.

SECTION 4.9.7: Biomarker Assays

Tumor tissue assessment of biomarkers will be assayed using IHC, ISH, qPCR gene expression profiling using microarray and mutation detection assays. Circulating Tumor DNA (ctDNA) in plasma samples may~~will~~ be assessed using a next generation sequencing approach (CAPP-Seq) to detect and quantitate lymphoma specific markers ~~(Newman et al. 2014).~~

SECTION 4.10.4: Activity Analyses

For patients ~~with DLBCL or FL~~ on obinutuzumab-containing cohorts, *primary response assessment for both DLBCL and FL will be* ~~primary assessment of tumor response will be~~ based on PET/CT scans *using the updated 2014 Lugano Response Criteria.* ~~Given the new Lugano Classification, 2014, criteria which recommend that complete response (PET-CR) be determined by PET-CT scan,scanResponse Criteria~~ as determined by an Independent Review *Committee*~~Facility~~ (IR*C*~~F~~). *P*~~p~~atients in Cohorts E, G, and H will be evaluated with a PET--CT scan at screening, between Cycle 4 Day 15 and Cycle 5 Day 1, and at *the end of treatment (*6-8 weeks after completing treatment*)*. The efficacy analysis for these cohorts will, therefore, be different from the analysis for Arms A-B and Cohorts C-D (Cheson, et al 2014) (see Appendix C-2). *Subsequent imaging can be CT only. Responses to study treatment will also be based on investigator assessments.*

SECTION 4.10.5: Exploratory Analyses

Frequencies and percentages of missing data for the PRO endpoints will be reported. Dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) will be summarized

~~Frequencies and percentages of missing data for the PRO endpoints will be reported. Dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) will be summarized~~.

SECTION 4.10.7: Determination of Sample Size

Therefore, up to 2*46*~~52~~ patients may be enrolled in this study.

SECTION 5.1.3: Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor

- Suspected transmission of an infectious agent by the study drug*, as defined below:*

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- *Tumor lysis syndrome (TLS) of any grade, irrespective of causality*
- ~~Grade ≥2 motor neuropathy~~
- ~~Grade ≥2 infusion reactions~~

SECTION 5.3.1.11: Pregnancy

If a female patient becomes pregnant while receiving the study drug or within *12*~~6~~ months after the last dose of *study treatment*~~investigational product~~, a Pregnancy Report eCRF should be completed within 24 hours of learning of the pregnancy. A pregnancy report will automatically be generated and sent to Genentech's Drug Safety Department or its designee. Pregnancy should not be recorded on the Adverse Event eCRF.

Male patients must also be instructed to immediately inform the investigator if their partner becomes pregnant during the study or within *5*~~6~~ months after the last dose of study drug. If such an event occurs, it should be reported as described below.

SECTION 5.4.1: Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product

Medical Monitor Contact Information for sites in North America:

Medical Monitor: [redacted] M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

~~Alternate Telephone No.: (888) 835-2555 (U.S. sites only)~~

SECTION 5.4.2: Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

Sites in Europe:

Fax No.: [redacted]

SECTION 5.6: Post-Study Adverse Events

France:

Fax No: 33 147617777

Email: neuilly.drug_safety@roche.com

Germany:

Fax No.: [redacted]

Email: grenzach.drug_safety@roche.com

Italy:

Fax No.: [redacted]

Email: monza.drug_safety@roche.com

Netherlands:

Fax No.: [redacted]

Email: woerden.drug_safety@roche.com

FIGURE 3a: Study Schema for Rituximab-Containing Arms/Cohorts *(Closed to Enrollment)*

FIGURE 3b: Study Schema for Obinutuzumab-Containing Arms/Cohorts

Figure 3b has been updated to reflect changes to the protocol.

REFERENCES

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol. 2014*;32:3059–68.* ~~Aug [cited 2014 Aug 29]. Available from: http://jco.ascopubs.org/content/early/2014/08/11/JCO.2013.54.8800.long.~~

APPENDIX A-3: Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H): Initial Study Treatment

Appendix A-3 has been updated to reflect changes to the protocol.

APPENDIX A-5: Study Flowchart: Post-Treatment Follow-Up for Obinutuzumab-Containing Regimens (Cohorts E, G-H)

Appendix A-5 has been updated to reflect changes to the protocol.

APPENDIX B-3: Serum and Plasma Pharmacokinetic, Blood Pharmacodynamic, and ATA Schedule for Obinutuzumab and DCDS4501A (Cohorts E, G-H)

Appendix A-5 has been updated to reflect changes to the protocol

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF PINATUZUMAB VEDOTIN (DCDT2980S) IN COMBINATION WITH RITUXIMAB OR POLATUZUMAB VEDOTIN (DCDS4501A) IN COMBINATION WITH RITUXIMAB AND A NON-RANDOMIZED PHASE IB/II EVALUATION OF POLATUZUMAB VEDOTIN IN COMBINATION WITH OBINUTUZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
EUDRACT NUMBER:	2011–004377–84
STUDY DRUG:	Pinatuzumab Vedotin (DCDT2980S); Polatuzumab Vedotin (DCDS4501A)
IND:	107713
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return a copy of the form to the CRO Monitor at your site. Please retain the original for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF PINATUZUMAB VEDOTIN (DCDT2980S) IN COMBINATION WITH RITUXIMAB OR POLATUZUMAB VEDOTIN (DCDS4501A) IN COMBINATION WITH RITUXIMAB AND A NON-RANDOMIZED PHASE Ib/II EVALUATION OF POLATUZUMAB VEDOTIN IN COMBINATION WITH OBINUTUZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
VERSION NUMBER:	*3*
EUDRACT NUMBER:	2011-004377-84
IND:	107713
STUDY DRUG:	Pinatuzumab Vedotin (DCDT2980S); Polatuzumab Vedotin (DCDS4501A)
PHASE:	II
INDICATION:	Relapsed or refractory B-cell NHL
SPONSOR:	Genentech, Inc.

Objectives

Primary Objectives

The primary objectives of this study are the following:

- To assess the safety and tolerability of the combination of DCDT2980S and rituximab administered to patients with relapsed or refractory follicular non-Hodgkin's lymphoma (NHL) and diffuse large B-cell lymphoma (DLBCL)
- To assess the safety and tolerability of the combination of DCDS4501A and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the safety and tolerability of the combination of DCDS4501A and obinutuzumab when administered to patients with relapsed or refractory follicular NHL or DLBCL
- To assess the anti-tumor activity of the combination of DCDT2980S and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and obinutuzumab in patients with relapsed or refractory follicular NHL and DLBCL *based on PET-CR at the end of treatment according to IRC per Lugano 2014 response criteria*

The secondary safety objectives of this study are the following:

- To assess the incidence of antibody formation to DCDT2980S, DCDS4501A*, and* obinutuzumab as measured by the formation of anti-therapeutic antibodies (ATAs)

- To compare the safety and tolerability of the combination of DCT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab

Activity Objectives

The secondary activity objective *for rituximab-containing arms* of the study is the following:

- To compare the anti-tumor activity of the combination of DCT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab

The secondary activity objectives for obinutuzumab-containing arms of the study are the following:

- *CR at end of treatment based on PET alone, as determined by the investigator*
- *Objective response (OR; CR or PR) at end of treatment based on PET alone as determined by investigator and IRC*
- *CR at end of treatment based on CT only as determined by the investigator and IRC*
- *OR at end of treatment based on CT only as determined by the investigator and IRC*
- *Best objective response (BOR, CR or PR) while on study based on PET alone or CT only, as determined by the investigator*

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives of this study are the following:

- To characterize the pharmacokinetics of DCDT2980S and rituximab in patients with relapsed or refractory NHL when the two drugs are given in combination
- To characterize the pharmacokinetics of DCDS4501A and rituximab or obinutuzumab in patients with relapsed or refractory NHL when the two drugs are given in combination

Patient-Reported Outcome Objectives

The objective of this study related to assessment of patient-reported outcomes (PRO) is the following:

- To assess patient-reported tolerability to study treatment and the impact of study treatment on patient functioning, on the basis of PRO *in Rituximab cohorts only*

Biomarker Objectives

The objectives of this study related to assessment of biologic markers are the following:

- To make a preliminary assessment of biologic markers that might act as predictors of DCDT2980S + rituximab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL
- To make a preliminary assessment of biologic markers that might act as predictors of DCDS4501A + rituximab or obinutuzumab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL

Study Design

Description of Study

This is a Phase Ib/II, multicenter, open-label study. Up to approximately 2*46* patients with relapsed or refractory FL and DLBCL will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data. Arms A and B and Cohort C are no longer enrolling patients.

For Obinutuzumab Cohorts:

Only investigational sites in the United States will enroll patients into Cohort E. Investigational sites in the United States *and worldwide* will participate in Cohorts G and H).

The study will be composed of a randomized portion and a non-randomized portion, as described in the protocol.

Rituximab-Containing Regimens with DCDT2980S or DCDS4501A

Randomized Portion of the Study (Arms A and B) – *Closed to Enrollment*

Following determination of eligibility, patients within each disease group will be randomized in a 1:1 ratio to receive one of two treatments:

- Arm A: Rituximab (375 mg/m^2) followed by DCDT2980S (2.4 mg/kg) every 21 days;
- Arm B: Rituximab (375 mg/m^2) followed by DCDS4501A (2.4 mg/kg) every 21 days

The first day of treatment constitutes Day 1 of each cycle. A typical cycle is 21 days in duration.

A dynamic hierarchical randomization scheme will be employed with respect to the following stratification factors:

- For patients with follicular lymphoma (FL) (see the protocol for definitions)

  Rituximab refractory disease (no response or disease relapse $<$ 6 months from last rituximab treatment) versus rituximab relapsed disease (disease relapse after response $\geq$ 6 months from last rituximab treatment)

- For patients with DLBCL (see the protocol for definitions)

  Second-line versus third-line (or beyond) therapy

  For second-line patients, disease relapse or no objective response (complete response [CR], unconfirmed CR [CRu], or partial response [PR]) <12 months from the start of initial therapy versus disease relapse, after initial objective response (CR, unconfirmed response [CRu] or PR), $\geq$ 12 months from start of initial therapy

  For third-line patients, failure to achieve a CR or progression < 6 months from start of most recent therapy versus CR or progression ≥ 6 months from start of most recent therapy

No formal testing comparing the two treatment arms in the randomized portion of the study is planned.

Non-Randomized Portion of the Study with Rituximab (Cohorts C and D) – ***Closed to Enrollment***

Only select investigator sites that have agreed to participate in the non-randomized portion of the study will enroll patients into these cohorts.

Patients with relapsed or refractory follicular NHL will be enrolled in Cohorts C and D to receive rituximab (375 mg/m^2) combined with DCDT2980S or DCDS4501A at a dose of 1.8 mg/kg. The first day of treatment constitutes Day 1 of each cycle. A typical cycle will be 21 days in duration.

The opening of either or both cohorts will be at the Sponsor's discretion and only after the enrollment of patients with FL into the randomized portion of the study is completed. Patients will not be randomized to receive one treatment or the other. It is anticipated that Cohort C and D will be opened sequentially.

All Patients on Rituximab-Containing Arms/Cohorts

All patients on rituximab-containing regimens, regardless of assigned arm/cohort, will receive DCDT2980S or DCDS4501A and rituximab administered by intravenous (IV) infusion on a 21-day cycle. For the first two cycles, rituximab will be administered by IV infusion on Day 1 and DCDT2980S or DCDS4501A will be administered by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this instance, rituximab will be administered first, followed by DCDT2980S or DCDS4501A. In certain circumstances—for example, infusion-related reactions (IRRs) requiring interruption or slowing of infusion rate—rituximab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDT2980S or DCDS4501A may be administered on Day 2 following completion of the rituximab infusion or on Day 3 of the cycle.

Patients may receive treatments for up to 1 year (17 cycles on an every-21-day schedule) if not discontinued because of significant toxicity, disease progression, or withdrawal from study.

Patients will be evaluated for safety and efficacy according to the Schedules of Assessments outlined in the protocol. Initial response assessments in this study will be performed every 3 months from the initiation of therapy until study treatment completion or early termination

(e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). Additional response assessments for patients who proceed to crossover treatment will be performed as described in the protocol; response assessments for patients who discontinue study treatment (both initially assigned treatment and crossover treatment) for reasons other than disease progression will be performed as described in the protocol.

Responses to study treatment will be based on investigator assessments. In addition, tumor assessment data will be transmitted to an Independent Review Facility (IRF) for collection and possible independent review.

Obinutuzumab-Containing Regimens with DCDS4501A (Cohorts E, G, and H)

DCDS4501A at 1.8 mg/kg will be given in combination with obinutuzumab to patients with relapsed or refractory follicular NHL and DLBCL in two stages: (1) safety run-in and (2) expansion.

Study treatment will be given in 21-day cycles for both follicular NHL and DLBCL. Patients will be treated for up to a total of 8 cycles. For the first cycle, obinutuzumab will be administered by IV infusion on Days 1, 8, and 15. DCDS4501A will be given on Day 2 for Cycle 1. In the absence of any infusion-related adverse events, obinutuzumab and DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the second cycle. If obinutuzumab and DCDS4501A are administered on the same day, the study drugs will be given sequentially. Obinutuzumab will be administered first, followed by DCDS4501A. In certain circumstances—for example, IRRs requiring interruption or slowing of infusion rate—obinutuzumab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDS4501A may be administered on Day 2 following completion of the obinutuzumab infusion.

Obinutuzumab-Containing Regimen in Phase Ib: Safety Run-In (Cohort E)

This portion of the study will consist of a safety run-in that will evaluate the safety of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in 6 patients (Cohort E). The safety run-in is described in detail in the protocol.

Obinutuzumab-Containing Regimens in Phase II: Expansion Stage (Cohorts G and H)

After the safety run-in has demonstrated that DCDS4501A at 1.8 mg/kg in combination with obinutuzumab is safe to administer, patients will be enrolled into two expansion cohorts based on histology of follicular NHL or DLBCL (Cohorts G and H respectively). Forty patients will be enrolled into each expansion cohort. An additional cohort(s) may be added in the future.

Follicular NHL Patients for Rituximab-Containing Arms/Cohorts

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed to regimens containing rituximab, defined as documented history of response (CR, CRu, or PR) of $\geq$ 6 months in duration from completion of all prior rituximab-containing regimens. A rituximab-containing regimen is defined as rituximab as a single agent during induction and/or maintenance or in combination with other agents during induction and/or maintenance.
- Refractory to any prior regimen containing rituximab, defined as no response to or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:

  Patients with progressive disease while receiving rituximab monotherapy, rituximab combined with chemotherapy, or rituximab maintenance therapy; patients must have received at least one full dose (375 mg/m^2) of rituximab.

  Patients with no objective response (PR or CR) to a rituximab-containing regimen consisting of at least 4 weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

  Patients with disease relapse, after having achieved an objective response, within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Enrollment of patients with refractory disease as defined above may be limited to no greater than 60% of the total follicular NHL cohort, in order to avoid overrepresentation of the refractory disease population.

Follicular NHL Patients for Obinutuzumab-Containing Cohorts

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed to prior regimen(s) after having a documented history of response (CR, CRu, or PR) of ≥ 6 months in duration from completion of regimen(s)
- Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy

DLBCL Patients for Rituximab-Containing Arms/Cohorts

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/stem cell transplant (SCT) will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) < 12 months from start of initial therapy (second-line refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response ≥ 12 months from start of initial therapy (second-line relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) < 6 months from start of prior therapy (third-line + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response ≥ 6 months from start of prior therapy (third-line + relapsed)

Enrollment into any of the above four categories may be limited to no greater than 40% of the DLBCL cohort—and to no more than 60% of the two refractory categories combined—in order to avoid overrepresentation of any specific subpopulation, refractory patients in particular.

DLBCL Patients for Obinutuzumab-Containing Cohorts

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/SCT as determined by the investigator will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) < 12 months from start of initial therapy (second-line refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response ≥ 12 months from start of initial therapy (second-line relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) < 6 months from start of prior therapy (third-line + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response ≥ 6 months from start of prior therapy (third-line + relapsed)

Crossover Treatment (Randomized Patients in Arms A and B Only)

Patients randomized to Arm A or Arm B who develop progressive disease may be eligible to receive crossover treatment consisting of rituximab and the other antibody-drug conjugate (ADC) or the other ADC alone—for example, Arm B treatment for patients who have disease progression while receiving Arm A treatment, and vice versa—provided the following conditions are met:

- Patients must not have experienced a toxicity requiring the discontinuation of DCDT2980S/DCDS4501A treatment OR experienced toxicity during the last dose of study treatment that would preclude treatment with the crossover regimen.

  Patients who had modifications to dosing and/or schedule on the initial study treatment will be permitted to receive crossover treatment in the absence of toxicities on the modified dose and/or schedule. The dose and schedule of crossover treatment will be determined by the investigator and the Medical Monitor.

Patients who had rituximab discontinued and continued on single-agent DCDT2980S/DCDS4501A treatment may receive crossover treatment of single-agent DCDS4501A/ DCDT2980S.

- Patients must have radiographically documented disease progression.
- Patients must meet all inclusion and exclusion criteria described in the Inclusion Criteria and Exclusion Criteria sections below, except for those related to prior rituximab treatment.
- Acceptable toxicity: All study drug–related adverse events from the initial study treatment must have decreased to Grade 1 or baseline grade on or before the first day of treatment on the crossover regimen. Exceptions may be allowed after a careful assessment and discussion of the benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.
- Administration of crossover treatment must be in the best interests of the patient as determined after a careful assessment and discussion of benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.
- A tumor biopsy (described in the protocol) will be required for patients with safely accessible site of disease, defined as requiring only local anesthesia and, in general, excluding the brain, lungs or any internal organs that may subject patients to significant risk.

  Patients for whom a safely accessible site of disease is not present may still receive crossover treatment without undergoing a biopsy. Eligibility to receive crossover treatment should be discussed with and approved by the Medical Monitor.

  A tumor biopsy of a safely accessible site of disease is optional for patients who are not eligible for study cross over.

Patients who are determined to be eligible for study cross over will be treated as follows:

- Assessments obtained at the initial study treatment discontinuation visit (described in the protocol) may be used as screening assessments for crossover treatment. The following re-screening assessments must be repeated/obtained within 1 week prior to starting treatment on the crossover regimen, in order to re-establish baseline pretreatment clinical and disease status: targeted physical exam, Eastern Cooperative Oncology Group (ECOG) status, and hematology and serum chemistry laboratory tests.

  Re-screening tests for hepatitis B and C do not need to be performed unless there is clinical suspicion of hepatitis B and/or C positivity.

  A radiographic tumor assessment must also be performed, unless already done to document disease progression, within 6 weeks prior to starting crossover treatment.
- Crossover treatment will begin no later than 42 days after the last dose of the prior study treatment.

Patients will be treated with the crossover treatment until a second disease progression event relative to the tumor assessment, documenting progressive disease on the initial study treatment, clinical deterioration, and/or intolerance to the crossover treatment for up to a maximum of 1 year (17 cycles on an every-21-day schedule). Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in the protocol. Response assessments for patients who discontinue study treatment for reasons other than disease progression will be performed as described in the protocol.

Clinical data and exploratory data derived from tumor biopsies obtained prior to crossover treatment will be monitored on an ongoing basis. Genentech has the right to restrict or suspend enrollment into crossover treatment at any time. Reasons for this may include, but are not limited to, the following:

- The incidence or severity of adverse events during crossover treatment indicates a potential safety hazard to patients.
- Patient enrollment into crossover treatment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Patients who are enrolled into the non-randomized portion of the study (Cohorts C, D, *E,* G, and H) will not have the option to receive crossover treatment upon disease progression.

Number of Patients

Up to approximately 2*46* patients with relapsed or refractory FL and DLBCL will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form(s)
- Age ≥ 18 years
- ECOG Performance Status of 0, 1, or 2
- Life expectancy of at least 12 weeks
- History of histologically documented relapsed or refractory Grades 1–3a FL or relapsed or refractory DLBCL
- Availability of an archival or freshly biopsied tumor tissue sample must be confirmed for study enrollment.
- Have a clinical indication for treatment as determined by the investigator
- Must have at least one bidimensionally measurable lesion (> 1.5 cm in its largest dimension by computed tomography [CT] scan or magnetic resonance imaging [MRI])
- Laboratory values (including patients with hepatic or renal involvement), as follows:

  AST and ALT $\leq 2.5 \times$ ULN

  Total bilirubin $\leq 1.5 \times$ ULN

  Platelet count $\geq 75{,}000/mm^3$ (unless thrombocytopenia clearly due to marrow involvement of NHL and/or disease-related immune thrombocytopenia)

  Absolute neutrophil count $\geq 1000/mm^3$ (without growth factor support, unless neutropenia clearly due to marrow involvement of NHL)

  Total hemoglobin ≥ 9 g/dL (without transfusion support > 14 days prior to screening, unless anemia clearly due to marrow involvement of NHL)

  Serum creatinine ≤ 2.0 mg/dL or measured creatinine CL ≥ 50 mL/min
- For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one highly effective form of nonhormonal contraception or two effective forms of nonhormonal contraception, **including at least one method with a failure rate of <1% per year**, through the course of study treatment and for $\geq$ 12 months after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab (whichever is later) in women and at least 5 months after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab (whichever is later) in men

  A woman is considered not to be of childbearing potential if she is postmenopausal, defined by amenorrhea of ≥ 12 months duration and age ≥ 45 years, or has undergone hysterectomy and/or bilateral oophorectomy.

  The following are considered highly effective forms of contraception: 1) true abstinence; 2) male sterilization (with post-procedure documentation of absence of sperm in the ejaculate). For female patients, the sterilized male partner should be the sole partner.

  The following are considered effective forms of contraception: 1) intrauterine device (IUD; copper IUD or hormonal IUDs only) or intrauterine system; 2) condom with spermicidal foam/gel/film/cream/suppository; 3) occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.

  Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S or, DCDS4501A or, rituximab, or obinutuzumab (whichever is later).

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Prior use of any MAb, radioimmunoconjugate or ADC within 4 weeks before Cycle 1, Day 1
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational anti-cancer agent within 2 weeks prior to Cycle 1, Day 1

  Adverse events except for sensory neuropathy from any previous treatments must be resolved or stabilized to Grade ≤ 2 prior to Cycle 1, Day 1.
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1, Day 1
- Prior allogeneic stem cell transplant
- Eligibility for autologous SCT (patients with relapsed or refractory DLBCL)
- History of transformation of indolent disease to DLBCL
- History of severe allergic or anaphylactic reactions to MAb therapy (or recombinant antibody-related fusion proteins)
- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma (e.g., of the cervix or breast) are allowed. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥ 2 years prior to Cycle 1, Day 1.
- Current or past history of CNS lymphoma
- Current Grade > 1 peripheral neuropathy
- Evidence of significant, uncontrolled, concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Recent major surgery within 6 weeks prior to Cycle 1, Day 1, other than for diagnosis
- Presence of positive test results for hepatitis B (HBsAg and/or total anti-HBc) or hepatitis C (HCV antibody)

  Patients who are positive for anti-HBc are eligible only if polymerase chain reaction (PCR) is negative for HBV DNA and it is believed by both the investigator and Medical Monitor that it is in the patient's best interest to participate.

  Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.
- Vaccination with a live vaccine within 28 days prior to treatment
- Known history of HIV seropositive status
- Women who are pregnant or lactating
- Ongoing corticosteroid use > 30 mg/day prednisone or equivalent

  Patients receiving corticosteroid treatment ≤ 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy

Length of Study

The length of study will be the time from screening of the first enrolled patient through 2 years after the Treatment Completion Visit for the last enrolled patient on an obinutuzumab-containing regimen. The length of the study for the obinutuzumab-containing cohorts is expected to be approximately 48 months.

End of Study

The end of study is defined as the timepoint at which patients enrolled in the obinutuzumab-containing regimens in the study have had at least 2 years of follow-up from the time of the Treatment Completion Visit or have discontinued from the study.

Outcome Measures

Safety Outcome Measures

The safety and tolerability of the combination of DCDT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab will be assessed using the following safety outcome measures:

- Incidence, nature, and severity of adverse events
- Incidence of anti-DCDT2980S*,* anti-DCDS4501A, or anti-obinutuzumab antibodies
- Changes in vital signs
- Changes in laboratory values

The determination of the DCDS4501A RP2D in combination with obinutuzumab will be assessed using the following primary safety outcome measures for the Phase Ib portion of the study:

- Incidence and nature of DLTs
- Incidence, nature, and severity of adverse events and serious adverse events
- Changes in vital signs, physical findings, ECGs, and clinical laboratory values during and following study treatment administration

Pharmacokinetic/Pharmacodynamic Outcome Measures

The following PK parameters will be derived from the serum concentration–time profiles of total antibody (the sum of conjugated and unconjugated antibody), including rituximab *or* obinutuzumab, and plasma concentration-time profiles of antibody-conjugated monomethyl auristatin E (acMMAE) and free MMAE following administration of DCDT2980S or DCDS4501A, when appropriate, as data allow:

- Total exposure (area under the concentration-time curve [AUC])
- Maximum plasma and serum concentration (C_{max})
- Clearance (CL)
- Terminal half-life ($t_{1/2}$)
- Steady-state volume of distribution (V_{ss})

Compartmental, non-compartmental, and/or population methods may be used. Other parameters, such as accumulation ratio and trough plasma and serum concentration (C_{min}), may also be calculated.

The following PD outcome measures will be assessed when appropriate, as data allow:

- Peripheral blood B-cell depletion and recovery. For each visit at which $CD19^+$ B-cell measurements are taken, B-cell data will be listed for each patient by dose level as follows:

  Absolute blood cell counts

  Percent change relative to the baseline blood counts

  $CD19^+$ B-cell recovery, defined as the timepoint when the values return to baseline levels or $\geq$50% of baseline levels

Activity Outcome Measures

The following activity outcome measures will be assessed *for rituximab-containing arms/cohorts (Arms A and B, Cohort C):*

- Objective response, defined as a PR or CR
- Duration of objective response, defined as the duration of time from the first occurrence of a documented objective response to time of relapse or death from any cause

- Progression-free survival (PFS), defined as the duration from initial randomization to the first occurrence of progression or death within 30 days of the last administration of study drug, whichever occurs first
- Overall survival (OS), defined as the duration from the date of randomization/enrollment to the date of death from any cause

Objective response and disease progression will be determined using standard criteria for NHL.

The following activity outcome measures will be assessed for obinutuzumab-containing cohorts (Cohorts E, G, and H) according to Lugano 2014 Response Criteria (Cheson et al. 2014):

The primary activity outcome measure will be assessed by:

- *CR at end of treatment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) based on PET alone, as determined by the IRC*

The following secondary efficacy outcome measures will be assessed:

- *OR (CR or PR) at end of treatment based on PET alone as determined by the investigator and IRC*
- *CR at end of treatment based on CT only, as determined by the investigator and IRC*
- *OR (CR or PR) at end of treatment based on CT only as determined by the investigator and IRC*
- *BOR (CR or PR) while on study based on PET alone or CT only, as determined by the investigator*

Exploratory Outcome Measures

The exploratory outcome measures will include, but will not be limited to, the following:

- Confirmation and quantitation of CD22, CD79b, and CD20 expression levels in either archival or freshly obtained (when available) tumor specimens (tumor biopsies, bone marrow biopsies, peripheral blood) by immunohistochemistry/flow cytometry/quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)
- Additional assessments related to the understanding of the mechanism of action of DCDT2980S, DCDS4501A, rituximab, and obinutuzumab, mechanisms of resistance to DCDT2980S, DCDS4501A, rituximab, and obinutuzumab, and/or NHL pathogenesis may be included.
- Treatment and disease symptom assessments using the M.D. Anderson Symptom Inventory (MDASI) *in rituximab-containing cohorts only*

The following exploratory efficacy outcome measures will be assessed:

- *DOR, defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse, or death from any cause, for the subgroup of patients with a best overall response of CR or PR, based on PET and/or CT scans as determined by the investigator assessment. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the DOR will be censored on the date of last disease assessment.*
- *PFS, defined as the time from date of randomization or first treatment (for G-containing arms) to the first occurrence of progression or relapse, or death from any cause , based on PET and/or CT scans as determined by the investigator assessment.*
- *EFS, defined as the time from date of randomization or first treatment (for G-containing arms) to any treatment failure including disease progression relapse, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first, based on PET and/or CT scans as determined by the investigator assessment*
- *OS, defined as the time from the date of first treatment to the date of death from any cause*

Investigational Medicinal Products

Test Product

Pinatuzumab Vedotin (DCDT2980S) and Polatuzumab Vedotin (DCDS4501A)

Patients will receive DCDT2980S or DCDS4501A at 1.8 mg/kg or 2.4 mg/kg by IV infusion on Day 1 or Day 2 for each cycle. The total dose of DCDT2980S or DCDS4501A for each patient

will be determined by the dose cohort to which the patient is assigned and depend on the patient's weight within 96 hours prior to Day 1 of each cycle.

Rituximab

All patients in rituximab-containing arms/cohorts will receive DCDT2980S or DCDS4501A and rituximab administered by IV infusion on a 21-day cycle. For the first two cycles, patients will receive rituximab 375 mg/m^2 by IV infusion on Day 1 and DCDT2980S or DCDS4501A by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab 375 mg/m^2 and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this case, rituximab will be administered first, followed by DCDT2980S or DCDS4501A.

Obinutuzumab

Patients in obinutuzumab-containing cohorts will receive DCDS4501A and obinutuzumab administered by IV infusion on a 21-day cycle. For the first cycle, patients will receive obinutuzumab 1000 mg by IV infusion on Days 1, 8, and 15. DCDS4501A will be given on Day 2 for Cycle 1. In the absence of any infusion-related adverse events, obinutuzumab and DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the second cycle.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

The final analysis will be based on patient data collected until all patients discontinue from the study or the study is terminated by the Sponsor, whichever occurs first. The analyses will be based on the safety evaluable population, defined as patients who received at least one dose of study treatment. All summaries will be presented according to the disease-specific cohort, treatment group, and assigned dose level.

Analysis of the Conduct of the Study

Enrollment, major protocol violations, and reasons for discontinuations from the study will be summarized.

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, duration of malignancy, and baseline ECOG Performance Status, will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables. All summaries will be presented overall and by treatment group, assigned dose level, and disease-specific cohort.

Study drug administration data will be listed by the disease-specific cohorts described in the protocol. Any dose modifications will be flagged. Means and standard deviations will be used to summarize the total doses of DCDT2980S, DCDS4501A, rituximab, and obinutuzumab received. All summaries will be presented by treatment group, assigned dose level, and disease-specific cohort.

Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, and changes in vital signs. All patients who receive any amount of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab will be included in the safety analysis and will be assigned to the treatment group on the basis of the study treatment received. Patients who have dose level changes from the initial assigned dose level will be summarized by the initial assigned dose level of DCDT2980S or DCDS4501A.

All adverse event data will be listed by study site, patient number, treatment group, disease-specific cohort, and cycle. All adverse events occurring on or after treatment on Day 1 of Cycle 1 will be summarized by mapped terms, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade. In addition, all serious adverse events, including deaths will be listed separately and summarized.

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to DCDT2980S and DCDS4501A will be summarized.

Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum concentrations of total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) and rituximab or obinutuzumab and plasma concentrations of acMMAE and free MMAE versus time data will be tabulated and plotted by NHL disease subtype (relapsed or refractory follicular NHL or DLBCL). The pharmacokinetics of the above analytes will be summarized by estimating the appropriate PK parameters (e.g., AUC, C_{max}, CL, V_{ss}, and $t_{1/2}$). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and range). Non-compartmental, compartmental, and/or population methods will be used, as data allow.

Exposure-response (safety and efficacy) analysis may be conducted with use of PK data and available drug effect (e.g., imaging, measures of tumor burden) and toxicity (e.g., clinical pathology) data, at the sponsor's discretion.

In addition, population PK methods may be employed to manage sparse data and to investigate the effects of certain covariates on the pharmacokinetics of DCDT2980S and DCDS4501A, as data allow, and at the sponsor's discretion.

Activity Analyses

Best overall response, duration of response, and PFS will be listed for all patients.

Overall response rate (ORR) from the initial study treatment will be calculated on the basis of data from patients who received study treatment. Objective response is defined as CR or PR as determined by the investigator, on the basis of physical examinations, radiographic scans, and bone marrow examinations, using modified response criteria for NHL and confirmed by repeat assessments $\geq$4 weeks after initial documentation. Any patient with insufficient data to determine response will be classified as a non-responder.

For patients with DLBCL, primary assessment of tumor response will be based on diagnostic imaging scans—for example, CT and/or MRI scans and positron emission tomography (PET) scans. For patients with FL enrolled on rituximab-containing arms/cohorts, primary assessment of response will be based on CT scans only; the assessment of response in FL based on PET scans will be performed for exploratory purposes only.

For patients on obinutuzumab-containing cohorts, *primary response assessment for both DLBCL and FL will be* based on PET/CT scans *using the updated 2014 Lugano Response Criteria. P*atients in Cohorts E, G, and H will be evaluated with a PET-CT scan at screening, between Cycle 4 Day 15 and Cycle 5 Day 1, and at *the end of treatment (*6-8 weeks after completing treatment). The efficacy analysis for these cohorts will, therefore, be different from the analysis for Arms A-B and Cohorts C-D. (Cheson, et al 2014) (see Appendix C-2). *Subsequent imaging can be CT only. Responses to study treatment will also be based on investigator assessments.*

Among patients with an objective response, duration of response will be defined as the time from the initial documentation of a CR or PR to the time of disease progression or death. If a patient does not experience death or disease progression before the end of the study, duration of response will be censored at the day of the last tumor assessment.

For the randomized portion of the study (Arms A and B), PFS is defined as the time from the date of randomization to the date of disease progression or death from any cause, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the date of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. For the non-randomized portion of the study (Cohorts C through H), PFS is defined as the time from the date of study enrollment to the date of disease progression or death from any cause, whichever occurs first.

For the randomized portion of the study (Arms A and B), OS is defined as the time from the date of randomization to the date of death from any cause. For the non-randomized portion of the study (Cohorts C through H), OS is defined as the time from the date of study enrollment to date of death from any cause.

Exploratory Analyses

Assay results of possible predictive markers will be listed by treatment group and response status.

Frequencies and percentages of missing data for the PRO endpoints will be reported. Dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) will be summarized.

Summary statistics of the MDASI items, scales, and their changes from baseline will be calculated at each assessment timepoint. The mean, standard error, and median of the absolute scores and the mean changes from baseline (and 95% CI) within and between study arms will be reported for the MDASI scales and single items, as well as the weekly averages of the worst symptom rating. For change scores in the MDASI from baseline, patients without baseline scores will not be included in the analyses. Line charts depicting the means and mean changes of subscales over time will be also provided.

Repeated measures mixed-effects models will explore MDASI subscale scores with a baseline score and appropriate covariates added, as appropriate.

Handling of Missing Data

For the endpoint of objective response, patients without a post-baseline tumor assessment will be considered non-responders in the all-treated population analysis.

For duration of response and PFS, data from patients who are lost to follow-up will be included in the analysis as censored observations on the last date that the patient is known to be progression free, defined as the date of the last tumor assessment, or, if no tumor assessments were performed, as the date of last study treatment plus 1 day.

Compliance to PRO data collection will be reported with summary statistics, including frequencies of reasons for non-compliance such as patient refusal to complete PRO data collection.

Determination of Sample Size

For the randomized portion of the study (Arms A and B), a target of 120 patients will be enrolled in two separate cohorts of patients (40 in the follicular NHL cohort and 80 in the DLBCL cohort). The randomized portion of this study is non-comparative in nature. No formal hypothesis testing is planned to compare the treatment arms. Moreover, there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms. Genentech has judged the proposed sample size to provide sufficient precision in estimating the anti-tumor activity of DCDT2980S combined with rituximab or DCDS4501A combined with rituximab as measured by objective response. For example, with the assumption of an observed response rate of 40%, a 90% confidence interval for the response rate would be approximately 22%–58% (i.e., 40% $\pm$ 18%) for the follicular NHL cohort and approximately 27%–53% (i.e., 40% $\pm$ 13%) for the DLBCL cohort. With 40 patients, there is an 87% chance of observing at least one adverse event with a true incidence of 5%.

For the non-randomized portions of the study (Cohorts C and D), approximately 20 patients will be enrolled into each arm, for a total of 40 patients. With 20 patients under an observed response rate of 40%, the exact Clopper-Pearson 90% confidence interval for the response rate would be 22%–61%. With respect to the assessment of safety based upon a sample size of 20 patients, the chance of observing at least one adverse event with a true incidence of 10% is 88%.

For the obinutuzumab safety run-in cohort (Cohort E), 6 patients will be enrolled. For the obinutuzumab expansion cohorts (Cohorts G and H), 40 patients with follicular NHL and 40 patients with DLBCL will be enrolled at the RP2D to further evaluate safety and efficacy of the combination. Table 3 in the protocol provides asymptotic 90% confidence intervals for the true probability of response for a range of observed proportions based upon a sample of 40 patients. A sample size of 40 patients is deemed sufficient to provide adequate precision on the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting rate of 45% assuming observed response rates of approximately 60% or higher (~24 responders observed among 40 patients).

Therefore, up to 252 patients may be enrolled in this study.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ac	antibody-conjugated
ADC	antibody–drug conjugate
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
anti-HBc	hepatitis B core antibody
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from 0 to infinity
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma and serum concentration
C_{min}	trough plasma and serum concentration
CR	complete response
CRu	unconfirmed response
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CVP	cyclophosphamide, vincristine, and prednisone
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC	ethics committee
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
FACS	fluorescence-activated cell sorting

Abbreviation	Definition
FBS	fasting blood sugar
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma
G	GA101 or obinutuzumab
G-CHOP	obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HNSTD	highest non-severely toxic dose
HPW	highly purified water
ICH	International Conference on Harmonisation
IgG1	immunoglobulin-G1
IHC	immunohistochemistry
IL	interleukin
IMC	Internal Monitoring Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
iNHL	indolent non-Hodgkin's lymphoma
IP	interferon-inducible protein
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	infusion-related reaction
ISH	in situ hybridization
IV	intravenous
IXRS	Interactive Voice and Web Response System
JC	John Cunningham
Kd	equilibrium dissociation constant
LC-MS/MS	liquid chromatography–tandem mass spectrometry
LMWH	low-molecular weight heparin
MCL	mantle cell lymphoma
MC-VC-PABC	maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl
MDASI	M.D. Anderson Symptom Inventory
MMAE	monomethyl auristatin E

Abbreviation	Definition
MAb	monoclonal antibody
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NK	natural killer
NOAC	new oral anticoagulant
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PE	polyethylene
PET	positron emission topography
PD	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PP	polypropylene
PR	partial response
PRO	patient-reported outcomes
PVC	polyvinyl chloride
PUR	polyurethane
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
q3w	every 3 weeks
R	rituximab
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RP2D	recommended Phase II dose
SAE	serious adverse event
SC	subcutaneous
SCID	severe combined immunodeficiency
SCT	stem cell transplant
SD	stable disease
SDV	source data verification
SmPC	Summary of Product Characteristics

Abbreviation	Definition
STD10	severely toxic dose to 10%
SWFI	Sterile Water for Injection
t1/2	terminal half-life
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
ULN	upper limit of normal
Vss	steady-state volume of distribution

1. BACKGROUND

1.1 BACKGROUND ON DISEASE

B-cell lymphoproliferative disorders are a heterogeneous group of malignancies, ranging from slow-growing indolent and incurable diseases with a median survival of 8–10 years (such as follicular non-Hodgkin's lymphoma [NHL]) to more aggressive intermediate- to high-grade lymphomas (such as diffuse large-cell lymphoma), which can have a median survival of 6 months if left untreated or long-term remission in more than 50% of patients with appropriate treatment. Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL accounting for approximately 30%–40% of all new patients, whereas follicular lymphoma (FL) accounts for approximately 20%–25% of new lymphomas.

Despite advances in the clinical outcomes of patients with NHL using treatments such as the CD20-specific monoclonal antibody (MAb) rituximab (Rituxan®, MabThera®) in combination with chemotherapy, indolent B-cell malignancies remain incurable, as do approximately half of aggressive NHL patients. Thus, there is still a need for treatments that can be combined with chemoimmunotherapy and can significantly extend disease-free and overall survival (OS) in these patients, with at least acceptable, if not superior, safety profiles.

1.2 BACKGROUND ON THE MOLECULES

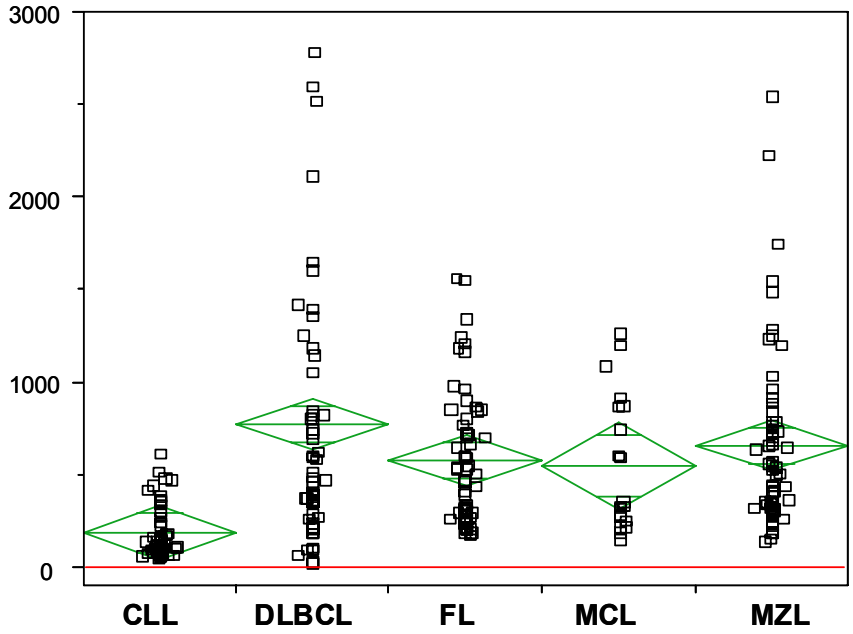
1.2.1 DCDT2980S

1.2.1.1 Background and Preclinical Data

CD22 is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of the B cell–derived malignancies, including nearly all NHL and chronic lymphocytic leukemia (CLL) samples tested (see Figure 1). Antibodies bound to CD22 are rapidly internalized, making CD22 ideally suited for targeted delivery of cytotoxic agents (Shan and Press 1995).

DCDT2980S is an antibody–drug conjugate (ADC) that consists of a potent anti-mitotic agent, monomethyl auristatin E (MMAE) conjugated to a humanized immunoglobulin-G1 (IgG1) anti-CD22 MAb, MCDT2219A, via a protease-labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl (MC-VC-PABC). MMAE has a mode of action similar to vincristine, which is a component of standard chemotherapy used in lymphoma therapy. This therapeutic approach takes advantage of the specific targeting capability of the antibody and the cytotoxic activity of MMAE. Following internalization, the MMAE is deconjugated from DCDT2980S by lysosomal enzymes, binds to tubulin, and disrupts the microtubule network, resulting in inhibition of cell division and cell growth and induction of apoptosis (Doronina et al. 2003).

Figure 1 CD22 Expression Levels on B-Cell Tumor Cells



CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MFI = mean fluorescence intensity; MZL = marginal zone lymphoma.
CD22 expression levels (MFI) on B-cell tumor cells were assessed by flow cytometry in patients diagnosed with the following B-cell lymphomas: CLL (n = 49), DLBCL (n = 59), FL (n = 58), MCL (n = 20), and MZL (n = 60).

Comprehensive pharmacologic, pharmacokinetic (PK), pharmacodynamic (PD), and toxicology evaluations were conducted to support the use of DCDT2980S in clinical trials. DCDT2980S binds human CD22 with a high affinity (equilibrium dissociation constant [K_d] = 1.7 ± 0.2 nM) and showed similar binding affinity to cynomolgus monkey CD22. No binding activity was observed with mouse and rat peripheral blood mononuclear cells (PBMCs).

The unconjugated antibody MCDT2219A did not appear to induce antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) in vitro. In contrast, DCDT2980S displayed potent and selective inhibition of cell proliferation in vitro (50% of the maximal inhibitory concentration [IC_{50}] = 0.33 nM) by cell viability assays. Efficacy studies conducted in murine xenograft models of human lymphoma (CD22-positive WSU-DLCL2 and BJAB cell lines) showed that a single dose of DCDT2980S resulted in regression of tumor growth at doses ranging from 1 to 4 mg/kg. PD studies with DCDT2980S showed that a single dose of 1–6 mg/kg resulted in partial depletion of peripheral blood B cells in cynomolgus monkeys with a corresponding depletion in germinal center B cells in lymphoid tissue.

The PK profiles of DCDT2980S were observed to be linear in rodents and moderately non-linear in cynomolgus monkeys over the tested dose range. The non-linear clearance (CL) observed in cynomolgus monkeys with DCDT2980S is likely due to the contribution of B cell-mediated CL to the total CL. The free MMAE concentrations in cynomolgus monkeys following DCDT2980S administration were generally 10,000 times lower than the concentration of DCDT2980S.

Cynomolgus monkeys were selected as the most relevant nonclinical species for the toxicology and PK/PD studies of DCDT2980S, given the comparable sequence homology of human and cynomolgus monkey CD22, similar binding affinity of DCDT2980S to human and cynomolgus monkey CD22, and comparable tissue cross-reactivity in both human and cynomolgus monkey tissues. DCDT2980S was well tolerated at doses of up to 3 mg/kg (highest non-severely toxic dose [HNSTD]) in monkeys and up to or greater than 10 mg/kg in rats (severely toxic dose to 10% [STD_{10}] of rats $\geq$ 10 mg/kg). Reversible bone marrow toxicity and associated hematopoietic changes were observed in both rats and monkeys treated with DCDT2980S or MMAE, suggesting that the toxicity of DCDT2980S is related to MMAE. Additional effects on liver and lung in rats were minimal in severity and reversible and did not occur in cynomolgus monkeys, which may be due to differences in species sensitivity, exposure, and/or pharmacokinetics.

Complete details of preclinical studies of DCDT2980S can be found in the DCDT2980S Investigator's Brochure.

1.2.1.2 DCDT2980S Clinical Data

a. Patient Enrollment

Both DCDT2980S monotherapy and combination therapy with rituximab have been studied in a Phase I study (Study DCT4862g) of patients with relapsed or refractory B-cell malignancies expected to express CD22, including indolent NHL, DLBCL, mantle cell lymphoma (MCL), and CLL.

All data presented herein is based on a data entry cutoff of 22 February 2013, with clinical data available from 65 patients with NHL (excluding patients with CLL) enrolled in dose-escalation and expansion cohorts. These include 49 patients who were treated with single-agent DCDT2980S at doses ranging from 0.1 to 3.2 mg/kg administered intravenously every 21 days and 16 patients who were enrolled into two Phase Ib cohorts with DCDT2980S administered at doses of 1.8 mg/kg (5 patients) and 2.4 mg/kg (11 patients) in combination with 375 mg/m^2 rituximab.

Enrollment into CLL dose escalation cohorts was closed on 31 May 2013. Refer to the DCDT2980S Investigator Brochure for details regarding clinical data in CLL patients.

b. Pharmacokinetics

The pharmacokinetics of DCDT2980S have been characterized in the Phase I Study DCT4862g. DCDT2980S was administered to patients with NHL at dose levels ranging from 0.1 to 3.2 mg/kg every 3 weeks (q3w). Three analytes were quantified: antibody-conjugated MMAE (acMMAE), total antibody, and free MMAE.

Preliminary PK analysis based on available data as of 22 June 2012 is summarized below.

The mean value of CL estimates of acMMAE and total antibody of each dose level for doses of ≥ 1.0 mg/kg ranged from 17.6 to 21.3 mL/day/kg and from 10.5 to 16.2 mL/day/kg, respectively. Similar CL estimates for doses ≥ 1.0 mg/kg suggested dose-proportional increase of acMMAE and total antibody exposure. CL estimates appeared to be slightly higher at doses < 1.0 mg/kg (0.1, 0.25, and 0.5 mg/kg), although data from these dose levels are limited. The CL of acMMAE was faster than that of total antibody at each dose level.

In patients with NHL, the mean value of the steady-state volume of distribution (V_{ss}) of acMMAE and total antibody of each dose level ranged from 69.2 to 130 mL/kg and from 97.4 to 154 mL/kg, respectively, across the dose levels tested, approximating human serum volume. V_{ss} values did not appear to change substantially with dose. The half-life for acMMAE and total antibody ranged from 2.9 to 7.0 days and from 4.4 to 13 days, respectively.

For acMMAE and total antibody, the time to maximum concentration occurred immediately after infusion. For free MMAE, the time to maximum concentration was approximately 2 to 3 days after infusion. Maximum plasma and serum concentration (C_{max}) and area under the concentration-time curve from Time 0 to infinity (AUC_{inf}) of free MMAE appeared to increase with dose across the dose levels tested. A half-life of 3-4 days for free MMAE was observed, which is relatively long and similar to that of its parent conjugate, suggesting formation rate–limited kinetics of free MMAE. No accumulation of free MMAE is expected for the q3w regimen. The C_{max} values of free MMAE in NHL patients were at least 100-fold lower than acMMAE concentrations at each dose level, suggesting a slow release of free MMAE from acMMAE and potentially fast elimination once it is formed.

Preliminary comparisons of pharmacokinetics between patients with NHL and CLL (for which patients are enrolled into separate dose-escalation cohorts) treated with identical doses of DCDT2980S provide some insight into the factors that affect pharmacokinetics. Both acMMAE and total antibody were cleared faster in CLL patients than in NHL patients. This observation is likely to be related to the high number of circulating B cells generally observed in CLL patients, which may result in significant target-mediated CL of DCDT2980S. The free MMAE exposure in CLL patients was relatively low compared to that of its parent conjugate.

The exposure parameters (C_{max} and AUC_{inf}) of total antibody, acMMAE, and free MMAE were similar between DCDT2980S and DCDT2980S + rituximab at doses of 1.8 and 2.4 mg/kg, based on preliminary data. This observation suggests that when given in combination, rituximab does not impact the pharmacokinetics of DCDT2980S; the effect of DCDT2980S on rituximab pharmacokinetics will be assessed.

All observations will be verified with additional data from the ongoing Phase I study as well as this study.

Refer to the DCDT2980S Investigator Brochure for complete and updated details.

c. Safety

Dose Limiting Toxicity

Study DCT4862g utilizes a standard 3+3 dose-escalation cohort enrollment scheme. Patients enrolled into each dose-escalation cohort in Study DCT4862g have been observed for dose-limiting toxicities (DLT) for a minimum of 21 days after their first dose of DCDT2980S. Any patient who did not complete the DLT observation period for any reason other than a DLT was replaced.

Separate dose-escalation cohorts enrolled patients with B-cell NHL and CLL. For the NHL dose escalation, DLTs of Grade 4 neutropenia occurred in 1 patient out of 3 DLT-evaluable patients in the 3.2 mg/kg single-agent cohort and 1 patient out of 11 DLT-evaluable patients in the 2.4 mg/kg + rituximab cohort. Consequently, DCDT2980S at 2.4 mg/kg was determined to be the recommended Phase II dose (RP2D) as both monotherapy and in combination with rituximab.

For the CLL dose-escalation cohorts, one DLT was reported to date. This Grade 5 event of febrile neutropenia resulted in the patient's death. Whereas the contribution of the study drug to the neutropenia could not be completely ruled out, other factors, including bone marrow involvement of disease that resulted in baseline anemia, thrombocytopenia and neutropenia, and clinical evidence of disease progression may have also played a contributory role.

Single-Agent DCDT2980S and DCDT2980S Combined with Rituximab in NHL

Forty-nine patients received single-agent DCDT2980S at a starting dose of $\geq$ 1.8 mg/kg (7 at 1.8 mg/kg, 42 at 2.4 mg/kg); 16 patients received DCDT2980S at a starting dose of $\geq$ 1.8 mg/kg in combination with rituximab (5 at 1.8 mg/kg, 11 at 2.4 mg/kg). Overall the safety profile of DCDT2980S combined with rituximab did not differ from that of single-agent DCDT2980S.

Treatment-emergent hematologic and commonly reported nonhematologic adverse events for all grades in patients treated with single-agent DCDT2980S and DCDT2980S plus rituximab included neutropenia (29%), febrile neutropenia (3%), infection (system organ class; 43%), anemia (25%), thrombocytopenia (12%), peripheral neuropathy

(28%), diarrhea (40%), pyrexia (14%), nausea (34%), and fatigue (55%). Treatment-emergent Grade ≥ 3 adverse events included neutropenia (25%), febrile neutropenia (3%), infection (system organ class; 11%), anemia (5%), peripheral neuropathy (3%), diarrhea (5%), pyrexia (2%), and fatigue (3%). Serious adverse events assessed by the treating investigator to be related to DCDT2980S were reported in 21% of patients. Dose discontinuations for adverse events were reported in 20% of patients.

Refer to the DCDT2980S Investigator's Brochure for complete and updated details related to safety.

d. Efficacy in Non-Hodgkin's Lymphoma

Investigator-based objective responses were observed in 17 of 43 (40%) patients treated with single-agent DCDT2980S and 5 of 15 (33%) patients treated with DCDT2980S combined with rituximab. Among patients with relapsed or refractory DLBCL, 11 of 28 (39%) objective responses (5 complete responses [CR] and 6 partial responses [PR]) were observed with single-agent DCDT2980S and 3 of 7 (43%; 2 CR, 1 PR) with DCDT2980S combined with rituximab. Among patients with relapsed or refractory indolent NHL (iNHL), 6 of 13 (46%) objective responses (2 CR, 4 PR) were observed with single-agent DCDT2980S and 1 of 4 (PR) with DCDT2980S combined with rituximab.

Refer to the DCDT2980S Investigator Brochure for complete and updated details related to anti-tumor activity.

1.2.2 DCDS4501A

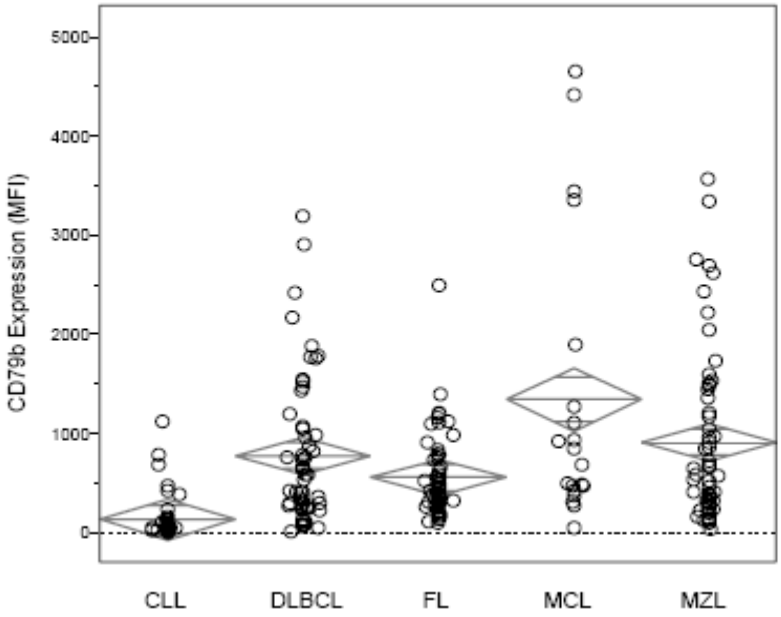
1.2.2.1 Background and Preclinical Data

CD79b is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of B cell–derived malignancies, including nearly all NHL and CLL samples tested (see Figure 2) (Dornan et al. 2009). Antibodies bound to CD79b are rapidly internalized, making CD79b ideally suited for targeted delivery of cytotoxic agents (Polson et al. 2007, 2009).

Similar to DCDT2980S, DCDS4501A is an ADC that contains a humanized immunoglobulin-G1 (IgG1) anti–human CD79b MAb (MCDS4409A) and MMAE linked through MC-VC-PABC.

Comprehensive pharmacologic, PK, PD, and toxicological evaluations were undertaken to support the entry of DCDS4501A into clinical trials. Because DCDS4501A specifically recognizes CD79b on B cells of human but not on those of cynomolgus monkey, rat, or mouse, a surrogate ADC (DCDS5017A) that binds to cynomolgus monkey CD79b was generated to assess the antigen-dependent pharmacological, toxicological, and PK/PD activities in cynomolgus monkeys. The structure, binding epitope, and binding affinity of the surrogate ADC are similar to those of DCDS4501A.

Figure 2 CD79b Expression Levels on B-Cell Tumor Cells



CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MFI = mean fluorescence intensity; MZL = marginal zone lymphoma.

CD79b expression levels (MFI) on B-cell tumor cells were assessed by flow cytometry in patients diagnosed with the following B-cell lymphomas: CLL (n = 49), DLBCL (n = 59), FL (n = 58), MCL (n = 20), and MZL (n = 60).

DCDS4501A bound human CD79b with high affinity ($K_d = 1.83 \pm 0.26$ nM); the surrogate ADC also showed similar high binding affinity to cynomolgus monkey CD79b. DCDS4501A displayed potent and selective inhibition of tumor cell proliferation in vitro ($IC_{50} = 0.071$ nM $\pm$ 0.01 nM) in cell viability assays. Moderate ADCC but no CDC activity was observed with the unconjugated clinical candidate antibody MCDS4409A. Both clinical and surrogate unconjugated antibodies showed no appreciable cytokine release when evaluated in in vitro cytokine release assays with PBMCs. Moderate elevations in interleukin (IL)-1α and interferon-inducible protein (IP)-10 were observed only with the unconjugated clinical antibody, however the clinical significance of these observations are not known because IL-1α and IP-10 are not produced by B cells, are not involved in B-cell signaling through CD79b, and are not associated with cytokine-release syndromes in vivo.

Single intravenous (IV) doses of DCDS4501A resulted in inhibition of tumor growth in murine xenograft models of lymphoma. Tumor regression was observed at doses ranging from 0.5 to 3 mg/kg. In contrast, MCDS4409A showed no activity. DCDS4501A administered at 5 mg/kg demonstrated better anti-tumor activity compared to a current standard-of-care regimen (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) in xenograft models of NHL. PD studies demonstrated that doses of the surrogate ADC ranging from 0.3 to 5 mg/kg resulted in a decrease of

peripheral blood B cells in cynomolgus monkeys. A preferential decrease of proliferating B cells ($CD20^+$ $Ki67^+$) compared to the resting B cells ($CD20^+$ $Ki67^-$)) by the surrogate ADC was demonstrated in cynomolgus monkeys, in line with the expected mechanism of action of an anti-mitotic agent, MMAE.

Due to B cell–mediated CL, non-linear pharmacokinetics were observed with the surrogate ADC in cynomolgus monkeys following single IV doses of 0.3–3 mg/kg or four doses of 3 and 5 mg/kg given q3w. The total antibody exposure after the fourth dose increased approximately 1.2- to 1.5-fold compared to the first dose. As expected, the toxicokinetic profile of the clinical ADC in rats and cynomolgus monkeys was linear in the tested dose range. Consistent with the half-life of the clinical ADC, minimal accumulation was observed following weekly dosing in rats and no accumulation was observed following q3w dosing in cynomolgus monkeys. The free MMAE concentrations in plasma following administration of the clinical or surrogate ADCs were generally low and overall did not exceed 2 ng/mL, regardless of dose. The overall incidence of anti-therapeutic antibodies (ATAs) was 20%–67% following administration of the clinical or surrogate ADCs in cynomolgus monkeys; however, the ATAs did not appear to impact the toxicokinetic/PK parameter estimates.

In repeat-dose toxicity studies in rats and cynomolgus monkeys, DCDS4501A and the surrogate ADC were well tolerated in monkeys up to doses of 5 mg/kg and 3 mg/kg respectively, with 3 mg/kg considered the HNSTD. In rats, DCDS4501A was well tolerated up to 6 mg/kg ($STD_{10} = 10$ mg/kg). The predominant antigen-independent findings associated with DCDS4501A or surrogate ADC exposure were reversible bone marrow toxicity and associated peripheral blood cell effects in both monkeys and rats. Administration of the surrogate ADC to monkeys also resulted in expected antigen-dependent reversible decreases in peripheral blood B cells and the disappearance of B-cell germinal centers in splenic lymphoid follicles at doses ≥ 3 mg/kg. Additional findings observed in rats but not in monkeys included thymic lymphoid depletion at ≥ 6 mg/kg, minimal to mild liver toxicities (at ≥ 6 mg/kg), lung toxicities at 10 mg/kg in male animals only, and a slight increase in apoptosis and mitoses in multiple tissues, including skin and adnexa. Hepatobiliary toxicity consisted of transient dose-dependent liver enzyme elevations accompanied by minimal to slight dose-dependent increases in mitotic figures/apoptosis in hepatocytes, sinusoidal cells, and bile duct epithelium as well as minimal to slight dose-dependent random focal hepatic necrosis. Pulmonary toxicity was characterized by minimal to slight dose-dependent alveolar macrophage infiltration, sometimes accompanied by minimal to slight type II pneumocyte hyperplasia/hypertrophy. These findings were consistent with the expected pharmacologic effect of MMAE on inducing mitotic arrest due to inhibition of tubulin polymerization. Except for two individual instances (one female given 10 mg/kg in the liver and one male given 10 mg/kg in the lung), these findings were completely reversible after a 6-week recovery period. Non-reversible male reproductive

toxicity, characterized by degeneration of testicular seminiferous tubules, was observed in rats at all doses.

Complete details of preclinical studies of DCDS4501A can be found in the DCDS4501A Investigator's Brochure.

1.2.2.2 DCDS4501A Clinical Data

a. Patient Enrollment

Both DCDS4501A monotherapy and combination therapy with rituximab are being studied in a Phase I study (Study DCS4968g) of patients with relapsed or refractory B-cell malignancies expected to express CD79b, including indolent NHL, DLBCL, MCL, and CLL.

All data presented herein is based on a data entry cutoff of 28 February 2013, with clinical data available from 60 patients with NHL (excluding patients with CLL) enrolled in dose-escalation and expansion cohorts. These include 51 patients who were treated with single-agent DCDS4501A ranging from 0.1 to 2.4 mg/kg administered intravenously every 21 days and 9 patients who were enrolled into a single Phase Ib cohort with DCDS4501A administered at a dose of 2.4 mg/kg in combination with 375 mg/m^2 rituximab.

In the CLL dose-escalation cohorts, two DLTs were reported at the single-agent dose of 1.8 mg/kg. Enrollment into the CLL cohorts was stopped on 7 January 2013. Refer to the DCDS4501A Investigator Brochure for details regarding clinical data in CLL patients.

b. Pharmacokinetics

The pharmacokinetics of DCDS4501A were characterized in the Phase I Study DCDS4501A. DCDS4501A was administered in patients with NHL at escalating doses of 0.1 to 2.4 mg/kg q3w as monotherapy and following administration of rituximab in the Phase Ib cohort. Three analytes were quantified: acMMAE, total antibody, and free MMAE.

Preliminary PK analysis based on available data as of 22 June 2012 is summarized below. The CL estimates of acMMAE and total antibody of each dose level is in the range of 14.9–21.2 mL/day/kg and 7.12–27.9 mL/day/kg, respectively. CL estimates were similar across doses of 0.1–2.4 mg/kg tested, suggesting dose-proportional increase of acMMAE and total antibody exposure. The CL of acMMAE was faster than that of total antibody at each dose level.

The mean value of V_{ss} of acMMAE and total antibody of each dose level ranged from 61 to 80.8 mL/kg and from 59.4 to 114.3 mL/kg, respectively, across the dose levels tested, which approximated human serum volume. V_{ss} values did not appear to change substantially with dose. The half-lives for acMMAE and total antibody are from 2.4 to 5.5 days and 2.9 to 7 days, respectively.

In a single-agent dose-escalation study, for acMMAE and total antibody, the time to maximum concentration occurred immediately after infusion. For free MMAE, the time to maximum concentration was approximately 2 to 3 days after infusion. C_{max} and AUC_{inf} of free MMAE appear increased with dose across the dose levels. A half-life of 3–4 days for free MMAE was observed, which is relatively long and similar to acMMAE and suggests formation rate–limited kinetics for free MMAE. No accumulation of free MMAE is expected for the q3w regimen. The C_{max} values of free MMAE in NHL patients were at least 100-fold lower compared with acMMAE concentrations at each dose level, suggesting a slow release of free MMAE from acMMAE and potentially fast elimination once it is formed.

Preliminary comparisons of pharmacokinetics between patients with NHL and CLL (for which patients are enrolled into separate dose-escalation cohorts) treated with identical doses of DCDS4501A provide some insight into the factors that affect pharmacokinetics. Both acMMAE and total antibody were cleared faster in CLL patients than in NHL patients. This observation is likely to be related to the high number of circulating B cells generally observed in CLL patients, which may result in significant target-mediated CL of DCDS4501A. The free MMAE exposure in CLL patients was relatively low compared with that of its parent conjugate.

To date, PK data for patients treated with DCDS4501A in combination with rituximab is limited. Consequently, full comparison with single-agent DCDS4501A pharmacokinetics is not possible. On the basis of very limited data from 3 patients, total antibody pharmacokinetics was comparable between 2.4 mg/kg of DCDS4501A administered as a single agent and following rituximab administration, suggesting that when given in combination, rituximab does not affect the pharmacokinetics of DCDS4501A; the effect of DCDS4501A on rituximab pharmacokinetics will be assessed.

All observations will be verified with additional data from the ongoing Phase I study as well as this study.

Refer to the DCDS4501A Investigator Brochure for complete and updated details.

c. Safety

Dose-Limiting Toxicities

Study DCS4968g utilizes a standard 3 + 3 dose escalation cohort enrollment scheme. Patients enrolled into each dose-escalation cohort in Study DCS4968g have been observed for DLTs for a minimum of 21 days after their first dose of DCDS4501A. Any patient who did not complete the DLT observation period for any reason other than a DLT was replaced.

DLT of Grade 4 neutropenia occurred in 1 patient out of 10 DLT-evaluable patients in the 2.4 mg/kg single-agent cohort and 1 patient out of 9 DLT-evaluable patients in the 2.4 mg/kg + rituximab cohort. Doses of DCDS4501A greater than 2.4 mg/kg as

monotherapy or in combination with rituximab were not assessed. Consequently, DCDS4501A at 2.4 mg/kg was therefore determined to be the RP2D as both monotherapy and in combination with rituximab.

In the CLL dose-escalation cohorts, two DLTs were reported at the single-agent dose of 1.8 mg/kg. One patient had a Grade 4 neutropenia, and 1 patient had a Grade 4 invasive fungal infection.

Single-Agent DCDS4501A and DCDS4501A Combined with Rituximab

Fifty-two patients received single-agent DCDS4501A at a starting dose of ≥ 1.8 mg/kg (6 at 1.8 mg/kg, 45 at 2.4 mg/kg); an additional 9 patients received DCDS4501A at a dose of 2.4 mg/kg in combination with rituximab. Overall, the safety profile of DCDS4501A combined with rituximab did not differ from that of single-agent DCDS4501A.

Treatment-emergent hematologic and commonly reported non-hematologic adverse events of all grades in patients treated with single-agent DCDS4501A and DCDS4501A plus rituximab included neutropenia (50%), febrile neutropenia (5%), infection (system organ class; 35%), anemia (13%), thrombocytopenia (18%), peripheral neuropathy (32%), diarrhea (43%), pyrexia (37%), nausea (35%), and fatigue (18%). Treatment-emergent Grade ≥ 3 adverse events included neutropenia (43%), febrile neutropenia (5%), infection (system organ class; 10%), anemia (8%), peripheral neuropathy (7%), diarrhea (3%), pyrexia (2%), and fatigue (5%). Serious adverse events assessed by the treating investigator to be related to DCDS4501A were reported in 20% of patients. Dose discontinuations for adverse events were reported in 33% of patients.

Refer to the DCDS4501A Investigator's Brochure for complete and updated details related to safety.

d. Efficacy

Investigator-based objective responses were observed in 28 of 49 (57%) patients treated with single-agent DCDS4501A and 7 of 9 patients (78%) treated with DCDS4501A combined with rituximab. Among patients with relapsed or refractory DLBCL, objective responses were observed in 16 of 30 (53%; 4 CR, 12 PR) patients treated with DCDS4501A; 1 patient with DLBCL was treated with DCDS4501A combined with rituximab and achieved a PR. Among patients with relapsed or refractory iNHL, objective responses were observed in 7 of 14 (50%; 2 CR, 5 PR) patients treated with single-agent DCDS4501A and 5 of 5 (100%; 2 CR, 3 PR) patients treated with DCDS4501A plus rituximab.

Refer to the DCDS4501A Investigator$'s$ Brochure for complete and updated details regarding anti-tumor activity.

1.2.3 Rituximab

Rituximab has been shown to be an effective treatment for CD20-positive B-cell malignancies and is commonly used both as a single agent and in combination with cytotoxic chemotherapy. Rituximab binds to CD20, a hydrophobic, transmembrane protein that is present on pre–B cells and mature B cells and in ≥ 90% of B-cell NHLs. It exerts its cytotoxic effects via complement-mediated B-cell lysis, ADCC, and induction of apoptosis (Cartron et al. 2004).

In the United States, rituximab has been approved by the U.S. Food and Drug Administration (FDA) for the following indications in NHL: as a single agent for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL; for the treatment of relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL, including initial treatment weekly for eight doses and re-treatment (weekly for four doses) in patients who responded to an initial course of rituximab; for the treatment of low-grade, CD20-positive B-cell NHL, in combination with cyclophosphamide, vincristine, and prednisone (CVP) induction chemotherapy in previously untreated patients with follicular, CD20-positive NHL; as treatment in previously untreated patients with low-grade, CD20-positive NHL who achieve an objective response or stable disease (SD) following CVP induction; and as maintenance therapy for previously untreated follicular CD20-positive B-cell NHL after achieving a response to a regimen including chemotherapy and rituximab.

In the European Union, rituximab (MabThera®) is approved for the treatment of the following indications in NHL: treatment of patients with Stage III–IV follicular NHL who are chemotherapy-resistant or in their second or subsequent relapse after chemotherapy; treatment of patients with CD20-positive DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy; as front-line therapy in Stage III–IV follicular NHL in combination with CVP chemotherapy; as maintenance therapy in patients with relapsed or refractory, follicular NHL responding to induction treatment with CHOP or R-CHOP; and as maintenance treatment for patients with FL who have responded to initial treatment with rituximab plus chemotherapy.

Rituximab has also been approved for the treatment of CLL. The European Medicines Agency (EMA) granted an approval for the use of rituximab in combination with chemotherapy for previously untreated CLL. The FDA approved the use of rituximab in combination with fludarabine and cyclophosphamide for patients with previously untreated and previously treated CD20-positive CLL.

Refer to the Rituximab *Investigator's Brochure* for complete details regarding clinical data related to approved indications. For rituximab safety information, refer to local rituximab prescribing information.

1.2.4 Obinutuzumab

1.2.4.1 Obinutuzumab Mechanism of Action

Obinutuzumab ([G], also known as RO5072759, GA101, Gazyva™, and Gazyvaro™) is a humanized type II and glycoengineered anti-CD20 MAb, derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics (Mössner et al. 2010; Golay et al. 2013):

- High-affinity binding to CD20 antigen on B cells
- Type II binding mode to the CD20 antigen, leading to a more even distribution of bound antibody to the surface membrane of the B cell due to lack of CD20 translocation into lipid rafts after antibody binding and low complement activation and low complement-dependent cytotoxicity related to the recognition of the CD20 epitope
- Compared with the type I anti-CD20 antibodies rituximab or ofatumumab, increased ADCC and antibody-dependent cell-mediated phagocytosis (ADCP) related to an improved binding of obinutuzumab to the different allotypes of FcγRIIIa and FcγRIIIb expressed by natural killer (NK) cells , monocytes/macrophages and neutrophils
- Compared with rituximab, increased direct cell-death induction related to an elbow hinge amino exchange of the Fab region and type II binding of the CD20 epitope

Obinutuzumab received FDA approval in November 2013 and EMA approval in July 2014 on the basis of the CLL-11 Study BO21004 for patients with relapsed Chronic Lymphocytic Leukemia. Obinutuzumab plus chlorambucil showed superiority over rituximab plus chlorambucil in all efficacy parameters such as overall response rate (ORR), complete remission rate (CRR), minimal residual disease (MRD), progression-free survival (PFS), event-free survival (EFS), and duration of response (DOR) (Goede et al. 2014).

Obinutuzumab is currently being explored in the treatment of lymphoid malignancies such as aggressive and indolent lymphomas (DLBCL, FL, and marginal zone lymphoma [MZL]). Preliminary data suggest possible increased anti-lymphoma efficacy over rituximab, a hypothesis that is currently being explored in several randomized trials, including a Phase III study of R-CHOP versus G-CHOP in first-line treatment of DLBCL, a Phase III study of R-chemotherapy (CHOP, CVP, or bendamustine) followed by rituximab maintenance compared with G-chemotherapy (CHOP, CVP, or bendamustine) followed by obinutuzumab maintenance in first-line treatment of FL and MZL, and a Phase III study of obinutuzumab combined with bendamustine compared with bendamustine in patients with rituximab-refractory indolent NHL.

1.2.4.2 Obinutuzumab Nonclinical Toxicology

The nonclinical toxicology of obinutuzumab has been evaluated in repeat-dose studies in cynomolgus monkeys given weekly IV (30-minute infusion) up to 26 weeks in duration and weekly SC injections for 4 weeks in duration. The high dose of 50 mg/kg in the 26-week study resulted in a steady-state area under the concentration-time curve from 0 to

24 hours (AUC_{0-24}) exposure of 341,000 μg•hr/mL, which is approximately 61-fold above that of the clinical exposure of 5584 μg•hr/mL.

Consistent with expected pharmacologic activity, obinutuzumab caused marked decreases in B cells, with corresponding lymphoid depletion in spleen and lymph nodes. Circulating CD40-positive mature B cells began to reverse after several months without treatment and maximally reversed to 7%–152% of baseline by 37 weeks. In addition, transient decreases in NK cells were observed; this finding is consistent with the pharmacologic effect of FcγRIIIa binding. Suspected opportunistic infections in as many as three unscheduled deaths were considered a possible secondary result of B-cell depletion.

Obinutuzumab was immunogenic in the cynomolgus monkey, which led to reduced systemic exposures in several animals and abrogation of the pharmacologic activity. Hypersensitivity reactions were noted that included systemic inflammation and infiltrates consistent with immune complex–mediated hypersensitivity reactions such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation and led to unscheduled termination in six animals.

Both the clinical IV formulation and the SC formulation of obinutuzumab were locally well tolerated across studies. No effects were present in male and female reproductive parameters included in the 26-week IV dose study. No obinutuzumab-related effects were observed on CNS, respiratory, or cardiovascular function.

In vitro assays using undiluted human whole blood measured significant increases in cytokine secretion caused by obinutuzumab, indicating that obinutuzumab has an increased propensity to trigger first infusion–related cytokine release in patients.

See the Obinutuzumab Investigator's Brochure for details on the nonclinical studies.

1.2.4.3 Obinutuzumab Nonclinical Efficacy

Obinutuzumab has in vivo efficacy superior to rituximab in various human lymphoma xenograft models. Both antibodies were tested in human SUDHL-4 cells (DLBCL model) injected subcutaneously in severe combined immunodeficient (SCID) beige mice. Rituximab administration was started when tumors were established and rapidly growing. Results showed that rituximab at 10 mg/kg inhibited tumor growth compared with rituximab at 1 mg/kg; however, increasing the rituximab dose to 30 mg/kg did not result in increased efficacy and rituximab was not able to achieve complete tumor regression. In contrast, obinutuzumab showed a dose-dependent increase in efficacy in the range of 1–30 mg/kg. Results showed complete tumor regression in all animals and lasting tumor eradication in 9 of 10 animals at the highest dose of 30 mg/kg and in 1 of 10 animals at a dose of 10 mg/kg.

In another experiment, SUDHL4 xenografts in SCID mice were first treated with weekly rituximab 30 mg/kg. When the tumors became refractory to rituximab (Day 35), rituximab treatment was continued or changed to either weekly vehicle control or obinutuzumab 30 mg/kg. While tumors in control- and rituximab-treated mice continued to grow, obinutuzumab-treated mice showed control of tumor growth and lived until Day 61 when control or rituximab-treated mice had already been sacrificed.

Additional studies have also shown similar results, with obinutuzumab treatment controlling tumor growth, whereas vehicle- and rituximab-treated tumors were not controlled (Mössner et al. 2010).

See the Obinutuzumab Investigator's Brochure for details on the nonclinical studies.

1.2.4.4 Obinutuzumab Clinical Experience

As of July 2013, more than 1900 patients with CD20-positive malignant disease have been treated with obinutuzumab in clinical trials. Clinical data for obinutuzumab are available from six clinical trials, including three Phase I and Phase II studies of obinutuzumab monotherapy, a Phase Ib chemotherapy combination study in NHL (Study BO21000), and two Phase III studies (Study BO21004 in CLL and Study GAO4753g in NHL).

Infusion-related reactions (IRRs), mostly Grades 1 and 2, are the most common adverse events observed during therapy. IRRs have been associated predominantly with the first infusion, generally occurring early during the infusion, shortly after the infusion, or, in some cases, up to 24 hours after the completion of the infusion. In a few patients, concurrent signs of laboratory tumor lysis syndrome (TLS) were observed. The incidence and intensity of IRRs decreased strongly with subsequent infusions of obinutuzumab. On the basis of preliminary observations, extensive tumor burden, tumor factors, and host factors may be predisposing factors for the occurrence of IRRs. The frequency and severity of IRRs is also reduced in lymphomas compared with CLL.

Other frequently observed adverse events include infections and neutropenia. Grade 3–4 thrombocytopenia and neutropenia, including febrile neutropenia, have been reported with obinutuzumab, associated predominantly with treatment of CLL rather than NHL. Given its anticipated mode of action, which results in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections during and after treatment.

Data from Study BO20999 (obinutuzumab monotherapy) showed safety and efficacy of single-agent obinutuzumab in patients with relapsed indolent and aggressive lymphomas. Responses were seen at both lower (400 mg) and higher (1600/800 mg) doses, although responses increased at the higher dose, with 54% of patients with indolent lymphoma and 32% of patients with aggressive lymphomas showing PR or CR at the end of treatment (EOT) (Morschhauser et al. 2013; Salles et al. 2013).

Study BO21000 (Phase Ib) evaluated obinutuzumab in combination with chemotherapy: obinutuzumab with fludarabine and cyclophosphamide and obinutuzumab with CHOP (Radford et al. 2013). Both chemotherapy combinations were shown to be feasible in patients with previously untreated or relapsed or refractory FL, with response rates of >90% for both regimens. Safety was acceptable, with no new or unexpected adverse events observed. The most common adverse event was neutropenia.

Data from obinutuzumab in combination with chlorambucil in CLL (Phase III Study BO21004) showed increased efficacy of this combination over rituximab-chlorambucil, with a hazard ratio of 0.39 for PFS. IRRs were common (65% all grades, 20% Grade 3–4, no fatal IRRs) and neutropenia occurred at increased frequency with the combination therapy (33% Grade 3–5), but there was no increase in infections or treatment-related deaths (Goede et al. 2014).

See the Obinutuzumab Investigator's Brochure for additional details on the clinical studies.

1.2.4.5 Obinutuzumab Pharmacokinetics and Pharmacodynamics

A two-compartment model comprising a time-varying CL pathway and a linear CL pathway provides an adequate description of the pharmacokinetics of obinutuzumab following IV administration in Study BO20999 and Study BO21003. Following the infusion of obinutuzumab, the elimination appears to be characterized by a linear CL pathway that is dependent on time (i.e., starting at a typical value of 630 mL/day and then gradually decreasing to an asymptote of 60 mL/day at steady state). Tumor burden may potentially contribute significantly to the CL of obinutuzumab, especially at the beginning of treatment when CD20-positive tumor cells are most abundant. As tumor burden decreases, the CL reaches an asymptote, which is considered to be primarily a function of the proteolytic metabolic CL. Some patients with a high tumor burden may appear to clear the drug from the plasma faster than patients with a low tumor burden because obinutuzumab binds to the CD20-positive tumor cells and is effectively removed from the plasma. The CL of the drug will vary with time because repeated treatments with obinutuzumab will reduce the quantity of CD20-positive tumor cells. The number of times obinutuzumab is administered during the first cycle of treatment may be expected to reduce the number of CD20-positive tumor cells, thus minimizing the impact of the time-varying CL pathway on obinutuzumab exposure.

Treatment with obinutuzumab resulted in extensive B-cell depletion, with all patients showing a reduction in B-cell counts to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before and after infusion, but transient increases occurring during the administration of obinutuzumab have been observed in the levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-10, and interferon (IFN)-γ.

1.3 RATIONALE FOR DOING THIS STUDY

The goals of this study are to continue to assess the safety, tolerability, and biologic and clinical activity of the combinations of DCDT2980S and rituximab and DCDS4501A and rituximab in two specific NHL patient populations: patients with relapsed or refractory follicular NHL and patients with relapsed or refractory DLBCL. An additional goal of this study is to assess the safety, tolerability, and potential biologic and clinical activity of DCDS4501A in combination with obinutuzumab, an anti-CD20 antibody, in the aforementioned NHL patient populations. These patients continue to have an extremely poor prognosis with no curative options available. Consequently, new therapeutic options are needed.

DCDT2980S, DCDS4501A, rituximab, and obinutuzumab each target antigens specific to B-cell malignancies including follicular NHL and DLBCL (see Figures 1 and 2).

The randomized component of the Phase II study design permits an assessment of the clinical benefit provided by each of these molecules in combination with rituximab, which has established clinical activity in B-cell malignancies both as monotherapy and in combination with chemotherapy. Data from this study will help inform the feasibility of the combination regimens in earlier lines of therapy (e.g., as first-line therapy in newly diagnosed patients).

The non-randomized component of the study will further evaluate the safety and tolerability and clinical activity of DCDS4501A in combination with obinutuzumab in patients with relapsed or refractory follicular lymphoma or DLBCL and will also provide preliminary evidence as to which anti-CD20 agent, rituximab or obinutuzumab, in combination with DCDS4501A, provides a better benefit-risk profile in the target population being studied.

The feasibility of combining an ADC with rituximab has previously been tested clinically with the combination of another, different CD22-specific ADC, inotuzumab ozogamicin (CMC-544), with results suggesting that the addition of rituximab may have increased clinical activity without significant increase in toxicity over the ADC alone in patients with aggressive NHL (Fayad et al. 2006; Nam et al. 2009; Nina et al. 2010). As noted in Section 1.2.1 and Section 1.2.2, the combinations of DCDT2980S and rituximab, and DCDS4501A and rituximab have been shown to have acceptable safety in patients with relapsed or refractory NHL in the Phase I studies (Studies DCT4862g and DCS4968g).

Given the relatively poor prognosis of patients with relapsed or refractory hematologic malignancies that have failed standard therapies, the nonclinical toxicity profile associated with DCDT2980S and DCDS4501A treatment, and the clinical safety profile observed to date for both ADCs, the benefit-risk ratio of a clinical study of DCDT2980S and DCDS4501A, each combined with rituximab or obinutuzumab, is considered acceptable.

1.3.1 Rationale for Assessing ADC Dose of 1.8 mg/kg Combined with Rituximab in iNHL

On the basis of available Phase I data (see Section 1.2.1 and Section 1.2.2), both DCDT2980S and DCDS4501A as single agents and combined with rituximab have shown early signs of clinical activity in heavily pretreated patients with relapsed or refractory NHL. However, early evidence in the Phase I studies indicate that duration of study treatment may be limited by tolerability to ADC. Specifically, for both ADCs, peripheral sensory neuropathy has been identified as a known risk (see Section 3.4.3.5). Notably, 4 of 7 and 5 of 11 discontinuations for adverse events in Studies DCT4862g and DCS4968g, respectively, were the result of peripheral neuropathy.

Because of the chronic course and incurability of iNHL, treatment paradigms are increasingly emphasizing tolerability to treatment in addition to efficacy. As both DCDT2980S and DCDS4501A have shown single-agent activity at the 1.8 mg/kg dose level (Advani et al. 2012; Palanca-Wessels et al. 2012), the purpose of enrolling additional cohorts of patients with FL is to determine whether lower doses of ADC in combination with standard doses of rituximab result in improved tolerability while maintaining efficacy in FL.

In contrast to iNHL, treatment paradigms in relapsed or refractory aggressive lymphomas such as DLBCL continue to place a premium on anti-tumor activity and higher tolerance for treatment-related toxicity, given that *the* duration of disease control and survival are substantially shorter and that treatment options are extremely limited. Early Phase I data suggest lower rates of study treatment discontinuation for adverse events among patients with DLBCL compared with patients with iNHL. Taken together with anti-tumor activity observed to date, the benefit-risk profile of the currently tested ADC dose of *1.8* mg/kg is considered acceptable *to combine with rituxminab in the treatment of patients with iNHL.*

1.3.2 Rationale for Assessing DCDS4501A in Combination with Obinutuzumab in Relapsed or Refractory NHL

The development of next-generation anti-CD20–directed therapy may further enhance the efficacy of current standard regimens for NHL. Obinutuzumab, also known as RO5072759, GA101, and Gazyva™/Gazyvaro™, a novel type II and glycoengineered anti-CD20 antibody, has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). Obinutuzumab is currently being compared with rituximab in two large Phase III studies in patients with newly diagnosed DLBCL (Study BO21005) and with previously untreated iNHL, including FL (Study BO21223). Assuming these studies demonstrate greater clinical benefit with obinutuzumab- vs. rituximab-containing regimens, potentially altering the standard of care in NHL, it will be important to also assess the safety and efficacy of combining DCDS4501A with obinutuzumab-containing regimens.

The goals of the non-randomized portion of the Phase Ib study are to assess the safety, tolerability, and potential biologic and clinical activity of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in patients with relapsed or refractory follicular NHL or DLBCL. The RP2D, the Phase II dose-expansion portion of the study, will further evaluate the safety and tolerability and clinical activity of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in patients with relapsed or refractory follicular NHL or DLBCL.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objectives of this study are the following:

- To assess the safety and tolerability of the combination of DCDT2980S and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the safety and tolerability of the combination of DCDS4501A and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the safety and tolerability of the combination of DCDS4501A and obinutuzumab when administered to patients with relapsed or refractory follicular NHL or DLBCL
- To assess the anti-tumor activity of the combination of DCDT2980S and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and obinutuzumab in patients with relapsed or refractory follicular NHL and DLBCL *based on PET-CR at the end of treatment according to IRC per Lugano 2014 response criteria*

2.2 SECONDARY OBJECTIVES

2.2.1 Safety Objectives

The secondary safety objectives of this study are the following:

- To assess the incidence of antibody formation to DCDT2980S, DCDS4501A, and obinutuzumab as measured by the formation of ATAs
- To compare the safety and tolerability of the combination of DCT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab

2.2.2 Activity Objective

The secondary activity objective *for rituximab-containing arms* of the study is the following:

- To compare the anti-tumor activity of the combination of DCT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab

The secondary activity objectives for obinutuzumab-containing arms of the study are the following:

- *CR at end of treatment based on PET alone, as determined by the investigator*
- *Objective response (OR; CR or PR) at end of treatment based on PET alone as determined by investigator and IRC*
- *CR at end of treatment based on CT only as determined by the investigator and IRC*
- *OR at end of treatment based on CT only as determined by the investigator and IRC*
- *Best objective response (BOR, CR or PR) while on study based on PET alone or CT only, as determined by the investigator*

2.2.3 Pharmacokinetic Objectives

The PK objectives of this study are the following:

- To characterize the pharmacokinetics of DCDT2980S and rituximab in patients with relapsed or refractory NHL when the two drugs are given in combination
- To characterize the pharmacokinetics of DCDS4501A and rituximab or obinutuzumab in patients with relapsed or refractory NHL when the two drugs are given in combination

2.3 EXPLORATORY OBJECTIVES

2.3.1 *Efficacy Objectives*

The exploratory efficacy objectives for this study are to evaluate the long-term outcome of obinutuzumab-treated patients according to Lugano 2014 response criteria, as measured by the following:

- *Duration of response based on PET and/or CT scans*
- *Progression-free survival (PFS) based on PET and/or CT scans*
- *Event-free survival (EFS) based on PET and/or CT scans*
- *Overall survival*

2.3.2 Biomarker Objectives

The objectives of this study related to assessment of biologic markers are the following:

- To make a preliminary assessment of biologic markers that might act as predictors of DCDT2980S + rituximab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL
- To make a preliminary assessment of biologic markers that might act as predictors of DCDS4501A + rituximab or obinutuzumab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL

2.3.3 Patient-Reported Outcomes Objective

The objective of this study related to assessment of patient-reported outcomes (PRO) is the following:

- To assess patient-reported tolerability to study treatment and the impact of study treatment on patient functioning on the basis of PRO *in Rituximab cohorts only*

2.3.4 Crossover Treatment Objective

The objective of this study related to assessment of crossover treatment is the following:

- To preliminarily assess the safety, tolerability, and anti-tumor activity of DCDT2980S and DCDS4501A, either as a single-agent or in combination with rituximab, as crossover treatment following disease progression on initial study treatment. (Note: This objective applies only to patients enrolled in Arms A and B [see Section 3.1])

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

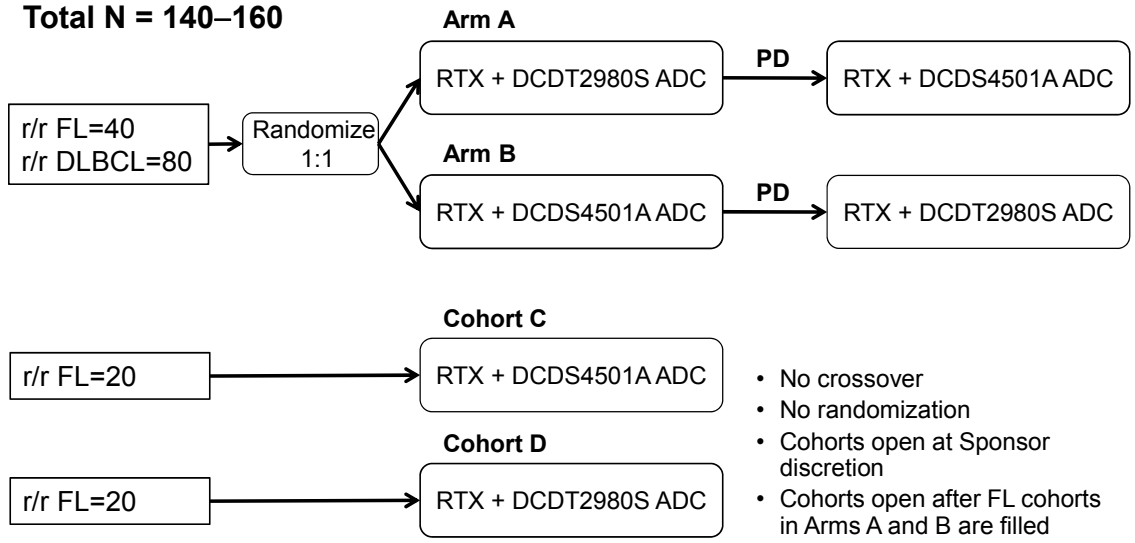
This is a Phase Ib/II, multicenter, open-label study. Up to approximately 2*46* patients with relapsed or refractory FL and DLBCL will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data. Arms A and B and Cohort C are no longer enrolling patients.

For Obinutuzumab Cohorts:

Only investigational sites in the United States will enroll patients into Cohort E. Investigational sites in the United States *and worldwide* will participate in Cohorts G and H.

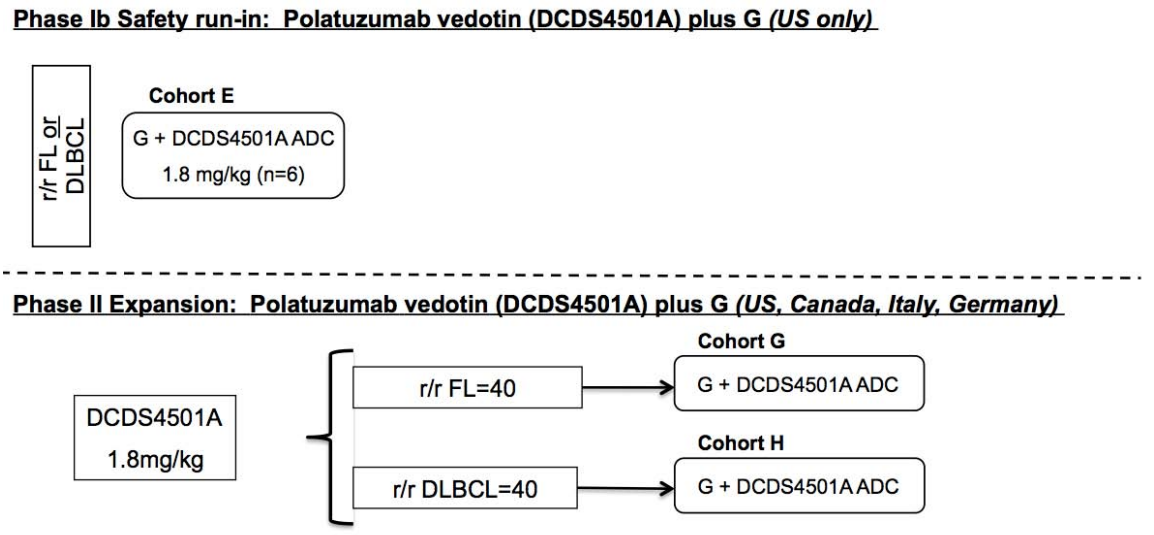
The study will be composed of a randomized portion and a non-randomized portion, as illustrated in Figure 3 .

Figure 3a Study Schema for Rituximab-Containing Arms/Cohorts ***(Closed to Enrollment)***



Arms A and B: RTX (375 mg/m^2) + ADC (2.4 mg/kg) administered in every-21-day cycles.
Cohorts C and D: RTX (375 mg/m^2) + ADC (1.8 mg/kg) administered in every-21-day cycles.

Figure 3b Study Schema for Obinutuzumab-Containing Arms/Cohorts



Cohorts E, G and H: Obinutuzumab (G) (1000 mg) D1, D8, D15 in Cycle 1, then D1 of each subsequent cycle.
Polatuzumab vedotin (DCDS4501A) (1.8 mg/kg) on D1. Cycles administered every 21 days.

ADC = antibody-drug conjugate; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; G = GA101/obinutuzumab; PD = progressive disease; r/r = relapsed or refractory; RTX = rituximab.

3.1.1 Rituximab-Containing Regimens with DCDT2980S or DCDS4501A

3.1.1.1 Randomized Portion of the Study (Arms A and B) – *Closed to Enrollment*

Following determination of eligibility, patients within each disease group will be randomized in a 1:1 ratio to receive one of two treatments:

- Arm A: Rituximab (375 mg/m^2) followed by DCDT2980S (2.4 mg/kg) every 21 days;
- Arm B: Rituximab (375 mg/m^2) followed by DCDS4501A (2.4 mg/kg) every 21 days

The first day of treatment constitutes Day 1 of each cycle. A typical cycle is 21 days in duration.

A dynamic hierarchical randomization scheme will be employed with respect to the following stratification factors:

- For patients with FL (see Section 3.1.4 for definitions)

  Rituximab refractory disease (no response or disease relapse $<$6 months from last rituximab treatment) versus rituximab relapsed disease (disease relapse after response $\geq$ 6 months from last rituximab treatment)

- For patients with DLBCL (see Section 3.1.5 for definitions)

  Second-line versus third-line (or beyond) therapy

  For second-line patients, disease relapse or no objective response (CR, unconfirmed CR [CRu], or PR) <12 months from the start of initial therapy versus disease relapse, after initial objective response (CR, unconfirmed response [CRu] or PR), $\geq$ 12 months from start of initial therapy

  For third-line patients, failure to achieve a CR or progression < 6 months from start of most recent therapy versus CR or progression ≥ 6 months from start of most recent therapy

No formal testing comparing the two treatment arms in the randomized portion of the study is planned.

3.1.1.2 Non-Randomized Portion of the Study with Rituximab (Cohorts C and D) – *Closed to Enrollment*

Only select investigator sites that have agreed to participate in the non-randomized portion of the study will enroll patients into these cohorts.

Patients with relapsed or refractory follicular NHL will be enrolled in Cohorts C and D to receive rituximab (375 mg/m^2) combined with DCDT2980S or DCDS4501A at a dose of 1.8 mg/kg. The first day of treatment constitutes Day 1 of each cycle. A typical cycle will be 21 days in duration.

The opening of either or both cohorts will be at the Sponsor's discretion and only after the enrollment of patients with FL into the randomized portion of the study is completed. Patients will not be randomized to receive one treatment or the other. It is anticipated that Cohort C and D will be opened sequentially.

3.1.2 All Patients on Rituximab-Containing Arms/Cohorts

All patients on rituximab-containing regimens, regardless of assigned arm/cohort, will receive DCDT2980S or DCDS4501A and rituximab administered by IV infusion on a 21-day cycle. For the first two cycles, rituximab will be administered by IV infusion on Day 1 and DCDT2980S or DCDS4501A will be administered by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this instance, rituximab will be administered first, followed by DCDT2980S or DCDS4501A. In certain circumstances—for example, IRRs requiring interruption or slowing of infusion rate—rituximab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDT2980S or DCDS4501A may be administered on Day 2 following completion of the rituximab infusion or on Day 3 of the cycle.

Patients may receive treatments for up to 1 year (17 cycles on an every-21-day schedule) if not discontinued because of significant toxicity, disease progression, or withdrawal from study.

Patients will be evaluated for safety and efficacy according to the Schedules of Assessments outlined in Appendices A-1, A-2, and A-4. Initial response assessments in this study will be performed every 3 months from the initiation of therapy until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). Additional response assessments for patients who proceed to crossover treatment (see Section 3.1.6) will be performed as described in Appendix A-2; response assessments for patients who discontinue study treatment (both initially assigned treatment and crossover treatment) for reasons other than disease progression will be performed as described in Appendix A-4.

Responses to study treatment will be based on investigator assessments. In addition, tumor assessment data will be transmitted to an Independent Review Facility (IRF) for collection and possible independent review.

3.1.3 Obinutuzumab-Containing Regimen with DCDS4501A (Cohorts E, G, and H)

DCDS4501A at 1.8 mg/kg will be given in combination with obinutuzumab to patients with relapsed or refractory follicular NHL and DLBCL in two stages: (1) safety run-in and (2) expansion.

Study treatment will be given in 21-day cycles for both follicular NHL and DLBCL. Patients will be treated for up to a total of 8 cycles. For the first cycle, obinutuzumab will be administered by IV infusion on Days 1, 8, and 15. DCDS4501A will be given on Day 2 for Cycle 1. In the absence of any infusion-related adverse events, obinutuzumab and DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the second cycle. If obinutuzumab and DCDS4501A are administered on the same day, the study drugs will be given sequentially. Obinutuzumab will be administered first, followed by DCDS4501A. In certain circumstances—for example, IRRs requiring interruption or slowing of infusion rate—obinutuzumab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDS4501A may be administered on Day 2 following completion of the obinutuzumab infusion.

3.1.3.1 Obinutuzumab-Containing Regimen in Phase Ib: Safety Run-In (Cohort E)

This portion of the study will consist of a safety run-in that will evaluate the safety of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in 6 patients (Cohort E). The safety run-in is described in detail in Section 3.4.

Obinutuzumab-Containing Regimens in Phase II: Expansion Stage (Cohorts G and H)

After the safety run-in has demonstrated that DCDS4501A at 1.8 mg/kg in combination with obinutuzumab is safe to administer, patients will be enrolled into two expansion cohorts based on histology of follicular NHL or DLBCL (Cohorts G and H, respectively). Forty patients will be enrolled into each expansion cohort. An additional cohort(s) may be added in the future.

3.1.4 Follicular NHL Patients for Rituximab-Containing Arms/Cohorts

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed as documented history of response (CR, CRu, or PR) of ≥6 months in duration from completion of all prior rituximab-containing regimens. A rituximab-containing regimen is defined as rituximab as a single agent during induction and/or maintenance or in combination with other agents during induction and/or maintenance.
- Refractory to any prior regimen containing rituximab, defined as no response to or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:

  Patients with progressive disease while receiving rituximab monotherapy, rituximab combined with chemotherapy, or rituximab maintenance therapy; patients must have received at least one full dose (375 mg/m^2) of rituximab.

Patients with no objective response (PR or CR) to a rituximab-containing regimen consisting of at least 4 weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Patients with disease relapse, after having achieved an objective response, within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Enrollment of patients with refractory disease as defined above may be limited to no greater than 60% of the total follicular NHL cohort, in order to avoid overrepresentation of the refractory disease population.

3.1.5 Follicular NHL Patients for Obinutuzumab-Containing Cohorts

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed to prior regimen(s) after having a documented history of response (CR, CRu, or PR) of $\geq$6 months in duration from completion of regimen(s)
- Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy

3.1.6 DLBCL Patients for Rituximab-Containing Arms/Cohorts

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/stem cell transplant (SCT) will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) $<$12 months from start of initial therapy (second-line refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response $\geq$12 months from start of initial therapy (second-line relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) $<$6 months from start of prior therapy (third-line + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response $\geq$6 months from start of prior therapy (third-line + relapsed)

Enrollment into any of the above four categories may be limited to no greater than 40% of the DLBCL cohort—and to no more than 60% of the two refractory categories combined—in order to avoid overrepresentation of any specific subpopulation, refractory patients in particular.

3.1.7 DLBCL Patients for Obinutuzumab-Containing Cohorts

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/SCT will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) $<$ 12 months from start of initial therapy (second-line refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response $\geq$ 12 months from start of initial therapy (second-line relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) $<$ 6 months from start of prior therapy (third-line + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response $\geq$ 6 months from start of prior therapy (third-line + relapsed)

3.1.8 Crossover Treatment (Randomized Patients in Arms A and B Only)

Patients randomized to Arm A or Arm B who develop progressive disease may be eligible to receive crossover treatment consisting of rituximab and the other ADC or the other ADC alone—for example, Arm B treatment for patients who have disease progression while receiving Arm A treatment, and vice versa—provided the following conditions are met:

- Patients must not have experienced a toxicity requiring the discontinuation of DCDT2980S/DCDS4501A treatment OR experienced toxicity during the last dose of study treatment that would preclude treatment with the crossover regimen.

  Patients who had modifications to dosing and/or schedule on the initial study treatment will be permitted to receive crossover treatment in the absence of toxicities on the modified dose and/or schedule. The dose and schedule of crossover treatment will be determined by the investigator and the Medical Monitor.

  Patients who had rituximab discontinued and continued on single-agent DCDT2980S/DCDS4501A treatment may receive crossover treatment of single-agent DCDS4501A/ DCDT2980S.
- Patients must have radiographically documented disease progression.
- Patients must meet all inclusion and exclusion criteria described in Section 4.1.1 and Section 4.1.2, except for those related to prior rituximab treatment.
- Acceptable toxicity: All study drug–related adverse events from the initial study treatment must have decreased to Grade 1 or baseline grade on or before the first day of treatment on the crossover regimen. Exceptions may be allowed after a careful assessment and discussion of the benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.

- Administration of crossover treatment must be in the best interests of the patient as determined after a careful assessment and discussion of benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.
- A tumor biopsy (see Section 4.5.1.9) will be required for patients with safely accessible site of disease, defined as requiring only local anesthesia and, in general, excluding the brain, lungs or any internal organs that may subject patients to significant risk.

    Patients for whom a safely accessible site of disease is not present may still receive crossover treatment without undergoing a biopsy. Eligibility to receive crossover treatment should be discussed with and approved by the Medical Monitor.

    A tumor biopsy of a safely accessible site of disease is optional for patients who are not eligible for study cross over.

Patients who are determined to be eligible for study cross over will be treated as follows:

- Assessments obtained at the initial study treatment discontinuation visit (see Section 4.5.4) may be used as screening assessments for crossover treatment. The following re-screening assessments must be repeated/obtained within 1 week prior to starting treatment on the crossover regimen, in order to re-establish baseline pretreatment clinical and disease status: targeted physical exam, Eastern Cooperative Oncology Group (ECOG) status, and hematology and serum chemistry laboratory tests.

    Re-screening tests for hepatitis B and C do not need to be performed unless there is clinical suspicion of hepatitis B and/or C positivity.

    A radiographic tumor assessment must also be performed, unless already done to document disease progression, within 6 weeks prior to starting crossover treatment.
- Crossover treatment will begin no later than 42 days after the last dose of the prior study treatment.

Patients will be treated with the crossover treatment until a second disease progression event relative to the tumor assessment, documenting progressive disease on the initial study treatment, clinical deterioration, and/or intolerance to the crossover treatment for up to a maximum of 1 year (17 cycles on an every-21-day schedule). Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in Appendices A-2. Response assessments for patients who discontinue study treatment for reasons other than disease progression will be performed as described in Appendix A-4.

Clinical data and exploratory data derived from tumor biopsies obtained prior to crossover treatment will be monitored on an ongoing basis. Genentech has the right to restrict or suspend enrollment into crossover treatment at any time. Reasons for this may include, but are not limited to, the following:

- The incidence or severity of adverse events during crossover treatment indicates a potential safety hazard to patients.
- Patient enrollment into crossover treatment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Patients who are enrolled into the non-randomized portion of the study (Cohorts C, D, E, G, and H) will not have the option to receive crossover treatment upon disease progression (see Section 3.2 for rationale).

3.2 RATIONALE FOR STUDY DESIGN

The primary rationale for the randomized non-comparative portion of the study is to assess clinical activity for the ADCs DCDT2980S and DCDS4501A in patients with relapsed or refractory NHL. The study design ensures that the patient populations under study are balanced with respect to critical variables such as prior therapy and ensures consistent clinical assessment of safety and efficacy. The collection and assessment of tumor tissue obtained prior to first study treatment and following progressive disease will provide further understanding of disease biology, possible mechanisms of resistance to the study treatment, and initial insights into tumor subtypes based on tumor biomarkers that are sensitive to study treatment. Finally, the inclusion of study treatment crossover (see Section 3.1.8) will address important questions regarding efficacy and tolerability of a second ADC-rituximab combination following disease progression on the initial ADC-rituximab combination.

The primary rationale for the non-randomized portion of the study (Cohorts C and D) is to assess the therapeutic index (i.e., the balance of efficacy and tolerability of DCDT2980S and DCDS4501A at a dose of 1.8 mg/kg in patients with relapsed or refractory follicular NHL). An informal comparison between patients with follicular NHL treated at the two doses of the ADC will help determine if tolerability is improved at the lower ADC dose without substantial compromise of efficacy.

The clinical feasibility of an ADC-rituximab combination regimen in patients with relapsed or refractory NHL has been previously studied. Results from studies of rituximab in combination with a different CD22-specific ADC, inotuzumab ozogamicin, demonstrated that when combined with rituximab, the ADC was able to be given at the single-agent MTD without the need for dose reduction of the ADC because of the lack of significant overlapping toxicity (Fayad et al. 2006; Nam et al. 2009; Nina et al. 2010).

DCDT2980S and DCDS4501A *were* both evaluated as single agents and in combination with rituximab in the Phase I studies Study DCT4862g and Study DCS4968g, respectively. Results from these trials have determined an MTD of 2.4 mg/kg for single-agent DCDT2980S and an RP2D of 2.4 mg/kg for single-agent DCDS4501A in

patients with mixed NHL. In addition, the RP2D of DCT2980S and DCDS4501 each in combination with rituximab (375 mg/m^2) on an every-21-day schedule was determined to be 2.4 mg/kg.

Study GO27834 will continue to assess the cumulative safety and longer-term tolerability of ADC-rituximab combination therapy. *Due to additional information about the benefit-risk profile of DCDS4501A at the 2.4 mg/kg dose, the Sponsor is no longer pursuing the 2.4 mg/kg dose of DCDS4501A in the obinutuzumab-containing cohorts.*

The primary rationale for the non-randomized Phase Ib/II obinutuzumab-containing cohorts (Cohorts E–H) is to assess safety and clinical activity for the combination of obinutuzumab and DCDS4501A in patients with relapsed/refractory NHL (Cohorts E, G, and H). Obinutuzumab (also known as RO5072759, GA101 and Gazyva™/Gazyvaro™), a novel type II and glycoengineered anti-CD20 antibody, has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). Obinutuzumab is currently being compared with rituximab in two large Phase III studies in patients with newly diagnosed DLBCL (Study BO21005) and previously untreated iNHL, including FL (Study BO21223). Assuming these studies demonstrate greater clinical benefit with obinutuzumab- vs. rituximab-containing regimens, potentially altering the standard of care in NHL, it will be important to also assess the safety and efficacy of combining DCDS4501A with obinutuzumab-containing regimens.

Study drug dosing will occur on Days 1 or 2 of each 21-day (or 28-day) cycle to allow for recovery from potential bone marrow toxicity.

3.2.1 Rationale for the PK Sample Schedule

PK data obtained in this study will be important in informing potential future trials with this combination. Given the likely changing effect of peripheral B-cell counts, tumor burden, and target antigen expression on target-mediated drug CL over multiple doses of DCDT2980S or DCDS4501A plus rituximab or obinutuzumab when the two drugs are given in combination, the drug levels of DCDT2980S or DCDS4501A-related analytes and rituximab or obinutuzumab will be assessed in this combination study.

In Studies DCT4862g and DCS4968g, single-agent DCDT2980S and DCDS4501A administered by IV infusion every 21 days were evaluated at doses ranging from 0.1 to 3.2 mg/kg for DCDT2980S and 0.1 mg/kg to 2.4 mg/kg for DCDS4501A in patients with NHL. Intensive PK sampling of all patients in the ongoing Phase I studies will provide sufficient data to allow complete profiling of the distribution and elimination phases for DCDT2980S and DCDS4501A and the investigation of potential correlations between various PK parameters and efficacy and/or toxicity. Consequently a reduced PK sampling scheme of DCDT2980S and DCDS4501A will be used in this study.

The PK data collected in this study will allow further characterization of the PK properties of DCDT2980S and DCDS4501A. In addition, the DCDT2980S and DCDS4501A concentration results from this study will be compared with available data from the

single-agent clinical studies to evaluate whether concurrent administration of rituximab affects the exposure of DCDT2980S and/or DCDS4501A.

Rituximab serum concentration measurements from this study will be compared with PK data from historical rituximab clinical studies to evaluate whether the combination with DCDT2980S and/or DCDS4501A affects the pharmacokinetics of rituximab.

Limited sampling of serum concentrations of obinutuzumab will be assessed and compared with historical data to evaluate potential PK interactions with DCDS4501A.

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety and tolerability of the combination of DCDT2980S and rituximab and DCDS4501A and rituximab or obinutuzumab will be assessed using the following safety outcome measures:

- Incidence, nature, and severity of adverse events
- Incidence of anti-DCDT2980S, anti-DCDS4501A, or anti-obinutuzumab antibodies
- Changes in vital signs
- Changes in laboratory values

3.3.2 Pharmacokinetic/Pharmacodynamic Outcome Measures

The following PK parameters will be derived from the serum concentration–time profiles of total antibody (the sum of conjugated and unconjugated antibody), including rituximab or obinutuzumab, and plasma concentration-time profiles of acMMAE and free MMAE following administration of DCDT2980S or DCDS4501A, when appropriate, as data allow:

- Total exposure (area under the concentration-time curve [AUC])
- Maximum plasma and serum concentration (C_{max})
- CL
- Terminal half-life ($t_{1/2}$)
- V_{ss}

Compartmental, non-compartmental, and/or population methods may be used. Other parameters, such as accumulation ratio and trough plasma and serum concentration (C_{min}), may also be calculated.

The following PD outcome measures will be assessed when appropriate, as data allow:

- Peripheral blood B-cell depletion and recovery. For each visit at which $CD19^+$ B-cell measurements are taken, B-cell data will be listed for each patient by dose level as follows:

  Absolute blood cell counts

  Percent change relative to the baseline blood counts

  $CD19^+$ B-cell recovery, defined as the timepoint when the values return to baseline levels or ≥ 50% of baseline levels

- Assessment of the kinetics of circulating tumor DNA

3.3.3 Activity Outcome Measures

The following activity outcome measures will be assessed *for rituximab-containing arms/cohorts (Arms A and B, Cohort C)*:

- Objective response, defined as a PR or CR
- Duration of objective response, defined as the duration of time from the first occurrence of a documented objective response to time of relapse or death from any cause
- PFS, defined as the duration from randomization to the first occurrence of progression or death within 30 days of the last administration of study drug, whichever occurs first
- OS, defined as the duration from the date of randomization/enrollment to the date of death from any cause

Objective response and disease progression will be determined using standard criteria for NHL (Cheson et al. 2007, 2014; see Appendix C-1 and Appendix C-2).

The following activity outcome measures will be assessed for obinutuzumab-containing cohorts (Cohorts E, G, and H) according to Lugano 2014 Response Criteria (Cheson et al. 2014):

The primary activity outcome measure will be assessed by:

- *CR at end of treatment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) based on PET alone, as determined by the IRC*

The following secondary efficacy outcome measures will be assessed:

- *OR (CR or PR) at end of treatment based on PET alone as determined by the investigator and IRC*
- *CR at end of treatment based on CT only, as determined by the investigator and IRC*
- *OR (CR or PR) at end of treatment based on CT only as determined by the investigator and IRC*
- *BOR (CR or PR) while on study based on PET alone or CT only, as determined by the investigator*

3.3.4 Exploratory Outcome Measures

The exploratory outcome measures will include, but will not be limited to, the following:

- Confirmation and quantitation of CD22, CD79b, and CD20 expression levels in either archival or freshly obtained (when available) tumor specimens (tumor biopsies, bone marrow biopsies, peripheral blood) by immunohistochemistry/flow cytometry/quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)
- Additional assessments related to the understanding of the mechanism of action of DCDT2980S, DCDS4501A, rituximab, and obinutuzumab, e.g., assessment of circulating tumor DNA(ctDNA) to monitor response, mechanisms of resistance to DCDT2980S, DCDS4501A, rituximab, and obinutuzumab, and/or NHL pathogenesis may be included.
- Treatment and disease symptom assessments using the M.D. Anderson Symptom Inventory (MDASI) *in rituximab-containing cohorts only*

The following exploratory efficacy outcome measures will be assessed:

- *DOR, defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse, or death from any cause, for the subgroup of patients with a best overall response of CR or PR, based on PET and/or CT scans as determined by the investigator assessment. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the DOR will be censored on the date of last disease assessment.*
- *PFS, defined as the time from date of randomization or first treatment (for G-containing arms) to the first occurrence of progression or relapse, or death from any cause , based on PET and/or CT scans as determined by the investigator assessment.*
- *EFS, defined as the time from date of randomization or first treatment (for G-containing arms) to any treatment failure including disease progression relapse, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first, based on PET and/or CT scans as determined by the investigator assessment*
- *OS, defined as the time from the date of first treatment to the date of death from any cause*

3.4 SAFETY PLAN

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

Safety will be evaluated through the monitoring of the following:

- Serious adverse events that are attributed to protocol-mandated interventions from the time of signing of the Informed Consent Form until the first dose of study treatment on Cycle 1, Day 1
- All adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab, whichever is later, including doses that were administered as part of crossover treatment

- All serious adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab, whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab, whichever is later, including doses that were administered as part of crossover treatment, and which are judged to be caused by DCDT2980S, DCDS4501A, rituximab, or obinutuzumab, regardless of time of onset
- Measurements of protocol-specified hematology and clinical chemistry laboratory values
- Measurements of protocol-specified vital signs
- Assessment of ECGs
- Assessment of physical findings on clinical physical examinations

Patients who have an ongoing study drug–related adverse event will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, it is determined that the study treatment or participation is not the cause of the adverse event, or the study is terminated.

See Section 5.2.3 for assessment of causality for adverse events.

3.4.1 Safety Run-In Analysis

As outlined in Figure 3b and Section 3.1.3.1, a safety run-in analysis (Cohort E) will be conducted by the Internal Monitoring Committee (IMC) to evaluate the combination of DCDS4501A at a dose of 1.8 mg/kg with obinutuzumab. This analysis will include data from the first 6 patients treated through *the safety observation period, from Cycle 1 Day 1 to Cycle 2 Day 1 for a minimum of 21days*. Three patients will initially be enrolled, and then an additional 3 patients will be enrolled after the first 3 patients have safely completed the first cycle. *The decision to enroll an additional 3 patients will be made by the Sponsor's Medical Monitor in consultation with the safety science leader, biostatistician, and participating investigators.* At the IMC's discretion, and at any point during enrollment of the safety run-in, a decision could be made that more than 6 patients are needed to evaluate safety. *Additional patients may also be enrolled at dose levels below 1.8 mg/kg of DCDS4501A (i.e., 1.4 mg/kg) based upon review of all safety data.*

Safety summaries will be assessed at the safety run-in for SAEs; Grade 3-5 treatment-related AEs; all AEs; all Grade 3-5 AEs; and AEs leading to treatment discontinuation or dose modification/interruption.

- During the 6-patient safety run-in, if any patient experiences a treatment-related death, then the obinutuzumab-containing portion of the study will be closed to further recruitment.

- During the 6-patient safety run-in:

  If 2 or more of the first 3 patients enrolled experience Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment

  If 1 of the first 3 patients enrolled experiences Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then an additional 3 patients will be recruited. If 2 or more of these first 3 patients experience Grade 4 febrile neutropenia or serious (i.e., SAE) infection with Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment.

  If 2 or more of the first 6 patients to be enrolled experiences Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment.

  Before the expansion portion of the study can begin (enrollment of Cohorts G and H), *s*ix patients must have completed *the safety observation period (Cycle 1 Day 1 to Cycle 2 Day 1 for a minimum of 21 days)* in the safety run-in (Cohort E).

3.4.2 Internal Monitoring Committee

This study will employ an Internal Monitoring Committee (IMC). The purpose of the IMC will be to make recommendations regarding study conduct on the basis of trial safety data to ensure patient safety while receiving study treatment.

The IMC will include *the Roche/Genentech Medical Monitor, at least one other Clinical Science representative who is not directly involved in the study*, a Drug Safety Scientist, a biostatistician, and a statistical programmer. Representatives from other Sponsor functional areas may be included as additional ad hoc members. In addition to the ongoing assessment of the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities by the Investigator and the Medical Monitor, the IMC will review the aforementioned data at least twice during the study.

Throughout the course of the study, the IMC will meet *at regular intervals during the study and* at the request of the Medical Monitor (e.g., on the basis of unexpected safety signals). The IMC may make recommendations regarding study conduct, including, but not limited to, performing additional safety analyses, amending the study protocol, holding patient enrollment to one or both treatment arms pending further safety evaluations, holding/discontinuing study treatment, or terminating the study.

Specific operational details such as the committee's composition, frequency and timing of meetings and members' roles and responsibilities will be detailed in the IMC charter.

For Arms A and B: The first planned review will occur after approximately 10 patients are randomized and have at least 6 weeks follow-up, and the next formal review will occur when approximately 60 patients are randomized and have at least 6 weeks follow-up.

3.4.3 Risks Associated with DCDT2980S and DCDS4501A

The clinical safety profile of DCDT2980S and DCDS4501A based on clinical data obtained in the ongoing Phase I studies are summarized in Section 1.2.1.2 and Section 1.2.2.2. Known and suspected risks, based on clinical data to date, are described below. Guidelines regarding the management of these risks through dose and schedule modifications are described in Section 4.3.1.3 and Section 4.3.1.4.

Refer also to the Investigator's Brochure for complete and updated details.

3.4.3.1 Infusion-Related Events

Some MAbs may be associated with the development of allergic or anaphylactic reactions, to either the active protein or excipients. True allergic or anaphylactic reactions are rare after the first dose of a product, as they require prior sensitization. Patients with true allergic or anaphylactic reactions should not receive further doses of the product.

MAbs may also be associated with reactions that are clinically indistinguishable from true allergic or anaphylactic reactions but are mediated through direct release of cytokines or other pro-inflammatory mediators. Such reactions are often termed IRRs. IRRs typically occur with the first infusion of a MAb product and are generally less frequent and/or less severe with subsequent infusions. They can often be managed by slowing the infusion rate and/or pre-treatment with various medications.

Allergic or anaphylactic reactions and IRRs typically begin during or within several hours of completing the infusion. The onset of symptoms may be rapid, and some reactions may be life threatening.

Patients should be monitored for these types of reactions during and after receiving DCDT2908S and DCDS4501A. DCDT2980S and DCDS4501A should be administered in an environment under close supervision of a physician and where full resuscitation facilities are immediately available. Specific guidelines for additional precautions to be taken during and following DCDT2980S and DCDS4501A administration are provided in Section 4.3.1.5.

3.4.3.2 Tumor Lysis Syndrome

There is a potential risk of TLS if treatment with DCDT2980S or DCDS4501A results in the rapid destruction of a large number of tumor cells. If any evidence of this occurs during the study, TLS prophylaxis measures will be instituted. Patients who are considered to have a high tumor burden (e.g., lymphocyte count $\geq 25 \times 10^9$/L) or bulky lymphadenopathy and who are considered to be at risk for TLS by the investigator will receive TLS prophylaxis (e.g., allopurinol $\geq$300 mg/day orally or a suitable alternative treatment according to institutional practice starting 12–24 hours prior to study treatment) and must be well hydrated prior to the initiation of study treatment at Cycle 1, Day 1. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion as deemed appropriate by the investigator.

3.4.3.3 Bone Marrow Toxicity/Neutropenia

Based on preclinical toxicity studies in rats and cynomolgus monkeys and clinical data from the ongoing Phase I Studies DCT4862g and DCS4968g, neutropenia has been identified as a known risk (adverse drug reaction) of both DCDT2908S and DCDS4501A. Neutropenia and neutropenia-associated events were reversible but in some cases resulted in protocol-mandated dose reductions and/or delays.

Adequate hematologic function should be confirmed before initiation of study treatment. Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Study treatment may be delayed or modified due to hematologic toxicities, as described in Section 4.3.1.

The use of G-CSF for neutropenia is described in Section 4.3.1.6. Transfusion support for anemia and thrombocytopenia is also permitted at the discretion of the treating physician.

Febrile neutropenia is commonly associated with myelotoxicity, which is considered a class effect of MMAE because it is commonly reported with ADCETRIS®, other similar ADCs, and vincristine sulfate.

Clinical data show that among the most common SAEs reported in both DCS4968g and DCT4862g studies were febrile neutropenia and pyrexia.

3.4.3.4 Immunogenicity

As expected with any recombinant antibody, DCDT2980S, DCDS4501A, and obinutuzumab may elicit an immune response and patients may develop antibodies against DCDT2980S, DCDS4501A, or obinutuzumab. Patients will be closely monitored for any potential immune response to DCDT2980S, DCDS4501A, and obinutuzumab. Appropriate screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with DCDT2980S, DCDS4501A,

and obinutuzumab. Considering the historically low immunogenicity rate of rituximab in NHL patients, ATAs against rituximab will not be monitored in this study.

3.4.3.5 Peripheral Neuropathy

On the basis of clinical data from the ongoing Phase I Studies DCT4862g and DCS4968g and data from brentuximab vedotin studies, an anti-CD30-vc-MMAE ADC (see Section 3.4.2), peripheral neuropathy (sensory and motor) has been identified as a known risk (adverse drug reaction) for both DCDT2980S and DCDS4501A.

Careful clinical evaluation of patients for neuropathy should be conducted prior to initiation of study drug. Patients should be monitored for signs of peripheral neuropathy or worsening neuropathy and appropriate action taken per protocol guidelines. Study treatment dose and schedule modifications for significant and prolonged neuropathic toxicity and dose-reduction are described in Section 4.3.1.7.

3.4.3.6 Reproductive Toxicity

Adverse effects on human reproduction and fertility are anticipated with the administration of DCDT2980S and DCDS4501A, given the mechanism of action of MMAE. Standard exclusion criteria will be used to ensure that patients of childbearing potential (male or female) are using adequate contraceptive methods.

3.4.3.7 Hyperglycemia

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other ADCs using the same vc-MMAE platform. Several patients given both DCDT2980S and DCDS4501A had abnormal fasting blood sugar (FBS) at screening with elevations of glucose following steroid administration prior to rituximab dose. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of anti-hyperglycemic medications. Emerging data suggest that hyperglycemia may occur more commonly in individuals with abnormal FBS values or known diabetes. This is also reported for ADCETRIS® (2013 SmPC and 2013 USPI).

3.4.3.8 Hepatotoxicity

Elevations in transaminase and/or bilirubin levels requiring dose modifications and treatment discontinuations have been reported in the ongoing clinical studies.

3.4.3.9 Commonly Reported Side Effects

Other commonly reported side effects of both DCDT2980S or DCDS4501A in the Phase I clinical trials and within this study include fatigue, nausea, decreased appetite, vomiting, hair thinning or loss, joint pains, loss of appetite, diarrhea, muscle aches, constipation, increases in blood glucose, and headaches.

3.4.4 Risks Associated with ADCETRIS® (Brentuximab Vedotin)

An ADC using the same MMAE drug and linker as that used in DCDT2980S and DCDS4501A, but coupled to an antibody targeting the CD30 antigen (brentuximab vedotin, ADCETRIS®, Seattle Genetics), was recently approved by the FDA for use in the treatment of specific subsets of patients with relapsed Hodgkin lymphoma and systemic anaplastic large-cell lymphoma.

The most common adverse reactions observed in studies with brentuximab vedotin (occurring in at least 20% of patients) were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting.

Serious adverse reactions were reported in 31% of patients receiving ADCETRIS®. The most common occurring in >2% of patients included peripheral motor neuropathy, abdominal pain, septic shock, supraventricular arrhythmia, pain in extremity, and urinary tract infection. In addition, John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has been reported.

Because of the use of the same MMAE drug, it is possible that the adverse events observed with the use of brentuximab vedotin can also be observed with the use of DCDT2980S and DCDS4501A.

Refer to the current version of the ADCETRIS® Prescribing Information for full and updated details.

3.4.5 Risks Associated with Rituximab Therapy and Their Management

3.4.5.1 Infusion Reactions

In single-agent clinical trials of rituximab and in post-marketing surveillance studies, mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first rituximab infusion. Other frequent infusion reaction signs and symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30–120 minutes of beginning the first infusion, and they resolved with slowing or interruption of the rituximab infusion and with supportive care (diphenhydramine, acetaminophen/paracetamol, IV saline, meperidine, and vasopressors). The incidence of infusion reactions was highest during the first infusion and decreased with each subsequent infusion.

Rituximab has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with a time to onset of 30–120 minutes. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm and may require

interruption of rituximab administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events (see Appendix D). Approximately 80% of fatal infusion reactions occurred in association with the first infusion of rituximab. Because of this, patients should receive premedication with acetaminophen/paracetamol, antihistamines, or corticosteroids, in accordance with standard clinical practice, prior to rituximab infusions.

3.4.5.2 Management of Severe Infusion Reactions

Administration of rituximab will occur in a setting with emergency equipment and staff who are trained to monitor for and respond to medical emergencies. The rituximab infusion should be interrupted for severe reactions on the basis of clinical judgment.

Medications and supportive care measures—including, but not limited to, epinephrine, antihistamines, glucocorticoids, IV fluids, vasopressors, oxygen, bronchodilators and acetaminophen/paracetamol—should be available for immediate use and instituted as medically indicated for use in the event of a reaction during administration.

In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during all rituximab infusions include those with preexisting cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events, and those with high numbers of circulating malignant cells ($\geq$25,000/μL) with or without evidence of high tumor burden.

3.4.5.3 Tumor Lysis Syndrome

Rapid reductions in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia have been reported within 12–24 hours after the first infusion of rituximab. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with rituximab. The risks of TLS appear to be greater in patients with high tumor burden. Patients deemed to be at high risk for TLS complications may, at the investigator's discretion, receive their initial dose of rituximab over 2 consecutive days (see Section 4.3.2.3). Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of TLS complications, rituximab has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

3.4.5.4 Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported for some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately

4 months after the initiation of rituximab and approximately 1 month after the last dose of rituximab. Patients with serologic findings consistent with chronic HBV (hepatitis B surface antigen [HBsAg] positivity) or hepatitis C virus (HCV) infection (HCV RNA or antibody positivity) are ineligible for this study. Patients who are not chronically infected with HBV but have serologic evidence of prior infection at baseline (IgG hepatitis B core antibody[anti-HBc] positive but HBV DNA negative) may be eligible (if believed to be in the patient's best interest by the investigator and Medical Monitor) and would be monitored closely for perturbations in liver function during the period of rituximab treatment and every 2–4 weeks thereafter. Such patients would also be required to receive prophylactic anti-viral therapy with lamivudine for at least 6 months after completion of rituximab therapy (Yeo et al. 2009).

Additional serious viral infections, new, reactivated, or exacerbated (e.g., infections caused by cytomegalovirus, varicella zoster virus, herpes simplex virus, West Nile virus, parvovirus B19, JC virus, and HCV) have been reported with rituximab, mainly in patients who had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Particular attention should be given to patients who have had significant prior immunosuppressive treatment such as high-dose chemotherapy and stem cell transplant. JC virus infection resulting in PML and death has been observed in rituximab-treated patients with hematologic malignancies or with autoimmune diseases. Most cases of PML were diagnosed within 12 months of the patient's last infusion of rituximab. Physicians should consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. Physicians should discontinue rituximab (and DCDT2980S and/or DCDS4501A) and consider discontinuation or reduction of any immunosuppressive therapy in patients who develop PML.

3.4.5.5 Cardiovascular Events

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with preexisting cardiac conditions, including arrhythmias and angina, who have had recurrences of these events during rituximab therapy should be monitored throughout the infusion and the immediate post-infusion period.

3.4.5.6 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, were observed in patients receiving rituximab in combination with chemotherapy for DLBCL. In post-marketing reports, which include patients with low-grade or follicular NHL and patients with DLBCL, the mean time to onset of symptoms was 6 days (range, 1–77 days) in patients with documented gastrointestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

3.4.5.7 Immunization

The safety of immunization with live viral vaccines following rituximab therapy has not been studied. Patients who participate in this study may not receive either primary or booster with live virus vaccines for at least *28 days* prior to initiation of rituximab or at any time during study treatment. Investigators should review the status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult with non-live vaccines intended to prevent infectious diseases prior to study therapy.

Refer to the Rituxan®/MabThera® (Rituximab) Package Insert/Summary of Product Characteristics (SmPC) for additional safety information.

3.4.6 Risks Associated with Obinutuzumab Therapy

No evidence available at the time of the approval of this protocol indicates that special warnings or precautions are appropriate other than those noted in the Obinutuzumab Investigator's Brochure and as described in the following sections.

3.4.6.1 Infusion-Related Reactions and Hypersensitivity Reactions (including Anaphylaxis)

The commonly experienced IRRs have been characterized by fever, chills, flushing, nausea, vomiting, hypotension, hypertension, fatigue, and other symptoms.

Respiratory infusion-related symptoms, such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema, have also been reported. These IRRs were mostly mild or moderate (NCI CTCAE v4.0, Grade 1 and 2 events), and $<$10% of the events were severe (Grade 3 events), occurring predominantly during the first hour of the infusion or shortly after the first infusion had finished. The events resolved with the slowing or interruption of the infusion and supportive care. The incidence and severity of IRRs decreased with subsequent infusions. Extensive tumor burden predominantly localized in the blood circulation (e.g., high peripheral lymphocyte count in patients with CLL) may be a predisposing factor for the development of IRRs.

IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions.

3.4.6.2 Tumor Lysis Syndrome

TLS has been reported with obinutuzumab administration. Patients with a high tumor burden, including patients with a lymphocyte count $\geq 25 \times 10^9$/L, particularly patients with B-cell CLL and MCL, are at increased risk for TLS and severe IRRs. All patients with peripheral blood lymphocyte counts of $\geq 25 \times 10^9$/L or bulky adenopathy must receive prophylaxis for TLS prior to the initiation of study treatment. This includes appropriate hydration, consisting of fluid intake of approximately 3 L/day, starting 1–2 days prior to the first dose of obinutuzumab, and administration of allopurinol (300 mg/day orally) or a suitable alternative (i.e., rasburicase) treatment, starting at least *12 –24* hours prior to the

first infusion of obinutuzumab (Cycle 1, Day 1). All patients should then be carefully monitored during the initial weeks of treatment. Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts $\geq 25 \times 10^9$/L) before the second and subsequent infusions of obinutuzumab should receive continuous TLS prophylaxis with allopurinol or a suitable alternative (i.e., rasburicase) and adequate hydration until the risk is abated, as determined by the investigator. *For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.*

3.4.6.3 Neutropenia

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. Use of G-CSF has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G-CSF is allowed for treatment of neutropenia in this study. Primary prophylaxis with G-CSF is recommended according to the American Society of Clinical Oncology (ASCO), European Organisation for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines, namely for patients who are ≥ 60 years old and/or with co-morbidities (Lyman et al. 2004).

3.4.6.4 Thrombocytopenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in patients treated with obinutuzumab. It seems that the first cycle is the greatest risk of hemorrhage in patients treated with obinutuzumab. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants), may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician.

3.4.6.5 Infection

On the basis of its anticipated mode of action, resulting in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Infections have been reported in patients receiving obinutuzumab. Therefore, obinutuzumab should not be administered to patients with active severe infections.

A “black-box” warning for obinutuzumab states that reactivation of hepatitis B as well as other serious viral infections (e.g., infections caused by cytomegalovirus, Varicella zoster virus, herpes simplex virus, JC virus, and HCV) that were new, reactivated, or exacerbated have been reported with the B cell–depleting antibody rituximab mainly in patients who had received the drug in combination with chemotherapy or as part of a hematopoietic SCT. The risk of such infections with obinutuzumab is unknown. Particular attention should be given to patients who have previously received significant immunosuppressive treatment, such as high-dose chemotherapy and SCT.

A “black-box” warning for obinutuzumab states that JC viral infection (including fatal) that resulted in PML with destructive infection of oligodendrocytes of the CNS white matte have been reported in patients treated with anti-CD20 therapies, including rituximab and obinutuzumab.

The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as cortical (e.g., aphasia or visual-spatial disorientation) can occur.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA).

Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the diagnosis and management of PML.

3.4.6.6 *Immunization*

The safety of immunization with live virus vaccines following obinutuzumab therapy has not been studied. Thus, vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

3.4.6.7 *Worsening of Preexisting Cardiac Condition*

In patients with underlying cardiac disease and treated with obinutuzumab, adverse events such as angina pectoris, acute coronary syndrome, myocardial infarction, heart failure, and arrhythmias, including atrial fibrillation and tachyarrhythmia, have been observed. These events may occur as part of an IRR and can be fatal. Therefore, patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution to prevent a potential fluid overload.

3.5 MINIMIZATION OF BIAS

For the randomized, non-comparative, open-label portion of the study, patients were randomly allocated to two treatment arms in a 1:1 ratio through use of an Interactive Voice and Web Response System (IXRS). A dynamic stratified randomization scheme was employed to ensure balance in the stratification factors as specified in Section 3.1. This portion of the study (Arms A and B) is now closed to enrollment.

3.6 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche group, will sponsor this study. A Contract Research Organization (CRO) will be utilized to perform project management, study management, and clinical monitoring. Genentech will conduct CRO oversight, approve patient eligibility, and perform dose escalation decision-making, medical monitoring, and statistical programming and analysis. An IMC (see Section 3.4) will provide an additional level of safety monitoring for the study.

Approximately 40 study centers in the United States, Canada, and Europe will participate in the study to enroll approximately 252 patients. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

Electronic data capture (EDC) will be utilized for this study. An IXRS will be used to assign patient numbers. A central laboratory will be used for sample management and storage until shipment to one of several specialty laboratories or Genentech for analysis. An IRF will be used for the collection and possible assessment of radiographic images from tumor assessments. Additional vendors for ECG collection and possible analysis and for PRO collection and data entry will be used.

3.7 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with the FDA regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws, as well as other applicable country laws.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria to be eligible for study entry:

- Signed Informed
- Consent Form(s)
- Age $\geq$ 18 years
- ECOG Performance Status of 0, 1, or 2
- Life expectancy of at least 12 weeks

- History of histologically documented relapsed or refractory Grades 1–3a FL or relapsed or refractory DLBCL
- Availability of an archival or freshly biopsied tumor tissue sample must be confirmed for study enrollment.
- Have a clinical indication for treatment as determined by the investigator
- Must have at least one bidimensionally measurable lesion (>1.5 cm in its largest dimension by computed tomography [CT] scan or MRI)
- Laboratory values (including patients with hepatic or renal involvement), as follows:

  AST and ALT $\leq 2.5 \times$ ULN

  Total bilirubin $\leq 1.5 \times$ ULN

  Platelet count $\geq 75{,}000/mm^3$ (unless thrombocytopenia clearly due to marrow involvement of NHL and/or disease-related immune thrombocytopenia)

  Absolute neutrophil count $\geq 1000/mm^3$ (without growth factor support, unless neutropenia clearly due to marrow involvement of NHL)

  Total hemoglobin ≥ 9 g/dL (without transfusion support >14 days prior to screening, unless anemia clearly due to marrow involvement of NHL)

  Serum creatinine ≤ 2.0 mg/dL or measured creatinine CL ≥ 50 mL/min
- For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one highly effective form of nonhormonal contraception or two effective forms of nonhormonal contraception, **including at least one method with a failure rate of < 1% per year**, through the course of study treatment and for ≥ 12 months after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab (whichever is later) in women and at least 5 months after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab (whichever is later) in men

  A woman is considered <u>not</u> to be of childbearing potential if she is postmenopausal, defined by amenorrhea of ≥ 12 months duration and age ≥ 45 years, or has undergone hysterectomy and/or bilateral oophorectomy.

  The following are considered highly effective forms of contraception: 1) true abstinence; 2) male sterilization (with post-procedure documentation of absence of sperm in the ejaculate). For female patients, the sterilized male partner should be the sole partner.

  The following are considered effective forms of contraception: 1) intrauterine device (IUD; copper IUD or hormonal IUDs only) or intrauterine system; 2) condom with spermicidal foam/gel/film/cream/suppository; 3) occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.

  Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab (whichever is later).

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Prior use of any MAb, radioimmunoconjugate or ADC within 4 weeks before Cycle 1, Day 1
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational anti-cancer agent within 2 weeks prior to Cycle 1, Day 1

  Adverse events except for sensory neuropathy from any previous treatments must be resolved or stabilized to Grade ≤ 2 prior to Cycle 1, Day 1.
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1, Day 1
- Prior allogeneic stem cell transplant
- Eligibility for autologous SCT (patients with relapsed or refractory DLBCL)
- History of transformation of indolent disease to DLBCL
- History of severe allergic or anaphylactic reactions to MAb therapy (or recombinant antibody-related fusion proteins)
- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma (e.g., of the cervix or breast) are allowed. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥ 2 years prior to Cycle 1, Day 1.
- Current or past history of CNS lymphoma
- Current Grade > 1 peripheral neuropathy
- Evidence of significant, uncontrolled, concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Recent major surgery within 6 weeks prior to Cycle 1, Day 1, other than for diagnosis
- Presence of positive test results for hepatitis B (HBsAg and/or total anti-HBc) or hepatitis C (HCV antibody)

Patients who are positive for anti-HBc are eligible only if PCR is negative for HBV DNA and it is believed by both the investigator and Medical Monitor that it is in the patient's best interest to participate.

Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.

- *Vaccination with a live vaccine within 28 days prior to treatment*
- Known history of HIV seropositive status
- Women who are pregnant or lactating
- Ongoing corticosteroid use $>$ 30 mg/day prednisone or equivalent

  Patients receiving corticosteroid treatment $\leq$ 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor via facsimile and obtain the Sponsor's approval to enroll the patient. Once the Sponsor reviews and approves the patient for enrollment, the patient number will be assigned via IXRS.

As described in Section 3.1.1.2, only select investigator sites that have agreed to participate in the non-randomized (Cohorts C and D) portion of the study will enroll patients into these cohorts. Cohorts C and D will be opened sequentially following completion of the randomized portion of the study for patients with FL.

For obinutuzumab-containing cohorts (Cohorts E, G, and H), patients with either relapsed or refractory follicular NHL or relapsed or refractory DLBCL will be enrolled. After the safety run-in stage for DCDS4501A at 1.8 mg/kg in combination with obinutuzumab, the *non-randomized dose-expansion portion of the study will enroll 40 relapsed or refractory FL* patients *into Cohort G and 40 relapsed or refractory DLBCL patients into Cohort H.*

Personnel responsible for performing PK and ATA assays will receive participants' treatment assignments to identify appropriate PK and ATA samples to be analyzed in the appropriate corresponding assays.

4.3 STUDY TREATMENT

4.3.1 DCDT2980S and DCDS4501A

4.3.1.1 Formulation and Storage

a. DCDT2980S

DCDT2980S will be provided as a lyophilized powder in a single-use 20-cc vial. The solution for reconstitution is Sterile Water for Injection (SWFI), and the reconstitution

volume is 2.6 mL to yield a final concentration of 20 mg/mL DCDT2980S in 40 mM L-histidine hydrochloride, 240 mM sucrose, and 0.02% polysorbate 20, pH 6.0.

Reconstituted DCDT2980S should be further diluted with sterile 0.9% NaCl to a total volume of 250 mL.

DCDT2980S vials must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. DCDT2980S should not be used beyond the expiration date provided by the manufacturer. Vial contents should not be frozen or shaken and should be protected from direct sunlight. After reconstitution, DCDT2980S vials may be stored at room temperatures (> 8°C–25°C [> 46°F–77°F]) for up to 4 hours or at refrigerated temperatures (2°C–8°C [36°F–46°F]) for up to 8 hours prior to use. Once DCDT2980S has been diluted with sterile 0.9% NaCl, the solution should be used within 4 hours at room temperature or within 8 hours at refrigerated temperature. Vials are intended for single use only; therefore, any remaining solution should be discarded.

For further details, refer to the DCDT2980S Investigator′s Brochure.

b. DCDS4501A

DCDS4501A is provided as a liquid formulation and contains no preservatives. Each single-use 20-cc vial is filled to deliver 100 mg of DCDS4501A. The drug product is formulated as 10 mg/mL DCDS4501A in 20 mM L-histidine acetate, 240 mM sucrose, 0.02% (w/v) polysorbate 20, pH 5.5.

DCDS4501A will be administered to patients intravenously via syringe pump with an IV infusion set containing a 0.22–µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight.

DCDS4501A vials must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. DCDS4501A vials may be stored at room temperature (> 8°C–25°C [46°F–77°F]) for up to 8 hours. DCDS4501A should not be used beyond the expiration date provided by the manufacturer. Vial contents should not be frozen or shaken and should be protected from direct sunlight. Vials are intended for single use only; therefore, any remaining solution should be discarded.

Once the DCDS4501A dose solution has been prepared, the solution should be used within 4 hours at room temperature (> 8 °C–25°C [46°F–77°F]) or within 8 hours refrigerated at 2°C–8°C (36°F–46°F). Because the drug product contains no preservatives, the Sponsor recommends using DCDS4501A in a syringe and extension set as soon as possible to reduce the risk of microbial contamination.

For further details, refer to the DCDS4501A Investigator Brochure.

4.3.1.2 Dosage and Administration

a. DCDT2980S-Specific Information

DCDT2980S will be administered to patients by IV infusion. Compatibility testing has shown that DCDT2980S is stable when diluted in polyvinyl chloride (PVC) bags to a concentration at or above 0.04 mg/mL in 0.9% NaCl diluent. The drug product will be delivered following dilution in 0.9% NaCl with a final DCDT2980S concentration determined based on dose and patient weight. The study drug will be diluted in a PVC bag and delivered using a 0.22 µm in-line filter on the IV infusion set.

Additional information/instructions regarding study drug administration will be provided in the Pharmacy Binder.

b. DCDS4501A-Specific Information

DCDS4501A will be administered to patients intravenously via syringe pump with an IV infusion set containing a 0.22 µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight. Compatibility testing has shown that DCDS4501A is stable both in syringes made of polypropylene (PP) and in standard extension sets with 0.22 µm in-line filter, when stored neat or diluted with 0.9% NaCl saline.

Additional information/instructions regarding study drug administration will be provided in the Pharmacy Binder.

c. General Information

The total dose of DCDT2980S and DCDS4501A for each patient will depend on the patient's weight within 96 hours prior to Day 1 of each cycle. The patient weight obtained during screening may be used for dose determination at all treatment cycles; if the patient's weight within 96 hours prior to Day 1 of a given treatment cycle differs by >10% from the weight obtained during screening, the new weight should be used to calculate the dose.

For both DCDT2980S and DCDS4501A, the initial dose will be administered to well-hydrated (based on clinical judgment) patients over 90 (±10) minutes. Premedication with acetaminophen or paracetamol (e.g., 500–1000 mg) and diphenhydramine (e.g., 50°C–100 mg) per institutional standard practice may be administered prior to each infusion. Administration of corticosteroids is permitted at the discretion of the treating physician. Patients who do not receive premedications prior to the first dose of DCDT2980S and who develop an IRR during the first dose should receive premedications prior to subsequent doses (see Table 1).

The DCDT2980S/DCDS4501A infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. Following the initial dose, patients will be observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If the infusion is well-tolerated, subsequent doses of

DCDT2980S/DCDS4501A may be administered over 30 (±10) minutes, followed by a 30-minute observation period post-infusion.

For instructions on study drug preparation and administration, refer to the DCDT2980S and DCDS4501A Investigator Brochure.

4.3.1.3 Dosage Modification

Patients should be assessed clinically for toxicity prior to each dose using the NCI CTCAE v4.0 grading scale. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable. If scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date, with subsequent dosing continuing on a 21-day schedule as applicable.

Specific guidelines around dosage modifications for neutropenia and peripheral neuropathy are detailed below in Section 4.3.1.6 and Section 4.3.1.7. Patients who experience other treatment-related Grade 3 or 4 toxicity or laboratory abnormalities will be allowed to delay dosing of study treatment (both ADC and rituximab or obinutuzumab) for up to 2 weeks to allow for recovery. Patients may continue to receive additional infusions of DCDT2980S or DCDS4501A per their treatment assignment provided that the toxicity has resolved to Grade ≤2 or ≥80% of the baseline value, whichever is lower, within the 2–week delay period. The decision for dose modification will be made on the basis of the investigator's assessment of ongoing clinical benefit with continued study treatment and in consultation with the Medical Monitor.

Once dose reductions of DCDT2980S or DCDS4501A are made for toxicity, dose re-escalation will not be allowed.

If a patient develops unacceptable toxicity to DCDT2980S or DCDS4501A, requiring its discontinuation, single-agent rituximab may be continued on the basis of the investigator's assessment of ongoing clinical benefit and with the approval of the Medical Monitor. Patients enrolled in obinutuzumab-containing cohorts will not continue on single-agent obinutuzumab unless approved by the Medical Monitor.

4.3.1.4 Schedule Modification

Patients in whom toxicities have not resolved to Grade ≤2 or ≥80% of baseline value, whichever is lower, may have their study treatment delayed by up to 2 weeks. Dosing of both DCDT2980S or DCDS4501A and rituximab or obinutuzumab should be held during this period. If all study drug–related toxicities have resolved sufficiently, the patient may resume DCDT2980S or DCDS4501A and rituximab or obinutuzumab dosing on the regular every-21-day schedule.

A patient's dosing may be changed to a 28-day cycle if it is felt by the investigator that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from a transient and reversible toxicity—for example,

cytopenia without requiring repeated treatment delays. Modifications to the dosing schedule in this fashion must be made in consultation with and with the approval of the Medical Monitor.

Patients who do not fulfill the criteria for continuation of dosing after the 2-week delay may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.6). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

Specific guidelines around schedule modifications for neutropenia and peripheral neuropathy are detailed below in Section 4.3.1.6 and Section 4.3.1.7.

4.3.1.5 Infusion Reaction

Patients will be monitored during and after each DCDT2980S/DCDS4501A infusion for 90 minutes after the first infusion and for 30 minutes after subsequent infusions in the absence of infusion-related adverse events. Patients who experience infusion-related symptoms should be managed as described in Table 1. Precautions for suspected anaphylactic reaction during study drug infusions are provided in Appendix D.

In the event of a life-threatening IRR, which may include pulmonary or cardiac events, or an IgE-mediated anaphylactic reaction, administration of DCDT2980S/DCDS4501A should be immediately discontinued. Patients who experience these reactions should receive aggressive symptomatic treatment and are not eligible to receive any additional study treatment.

Premedication prior to DCDT2980S/DCDS4501A with acetaminophen/paracetamol, antihistamines, or corticosteroids per standard clinical practice is permitted—for example, in patients with substantial tumor burden and where the risk of cytokine release syndrome is high. In patients who do not receive premedication prior to any given dose of DCDT2980S/DCDS4501A and who develop any Grade ≥ 2 infusion-related toxicity, premedication should be administered prior to subsequent doses.

Table 1 Management of Infusion-Related Symptoms for All Study Drugs

Infusion-Related Symptoms [a]	Guidance
Grade 1–2	• Slow or hold infusion • Give supportive treatment [b] • Upon symptom resolution, may resume/escalate infusion rate at the investigator's discretion [c] • Note: For Grade 2 wheezing or bronchospasm, patient must be premedicated for subsequent doses. If symptoms recur with the same or greater severity, the infusion must be stopped immediately and study treatment permanently discontinued.
Grade 3	• Discontinue infusion • Give supportive treatment [b] • Upon symptom resolution, may resume/escalate infusion rate at the investigator discretion [c] • Note: If the same adverse event recurs with the same or greater severity, treatment must be permanently discontinued. • Note: For Grade 3 hypotension or fever, patient must be premedicated before re-treatment. If symptoms recur, then study drug must be permanently discontinued. • Note: If patient has Grade 3 wheezing or bronchospasm at first occurrence, study treatment should be permanently discontinued.
Grade 4	• Discontinue infusion immediately, treat symptoms aggressively, and permanently discontinue patient from study treatment

IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Refer to the NCI CTCAE v4.0 scale for the grading of symptoms. Management of IgE-mediated allergic reactions should be as directed in the text preceding this table.

[b] Supportive treatment: Patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the last 4 hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators. Patients with hypotension requiring vasopressor support must be permanently discontinued from study drug.

[c] Infusion rate escalation after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hr every 30 minutes.

4.3.1.6 Neutropenia

Because neutropenia is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.3.3), the use of growth factor support (G-CSF) as prophylactic and therapeutic indications is permitted (see Appendix F) in order to allow continued dosing of DCDT2980S/DCDS4501A. Dose modifications for patients who experience treatment-related Grade 3–4 neutropenia in the context of G-CSF usage are as follows:

- Primary prophylaxis with G-CSF (i.e., prior to the first dose of DCDT2980S/DCDS4501A) is permitted for patients with clinical factors listed in

Appendix F or who otherwise are considered at high risk for developing neutropenia on study treatment.

- Patients who experience treatment-related Grade 3–4 neutropenia will be allowed to delay dosing of study treatment (both ADC and rituximab or obinutuzumab) for up to two weeks to allow for recovery. Therapeutic G-CSF is permitted as clinically indicated (see Appendix F) and to facilitate neutrophil recovery to allow subsequent DCDT2980S/DCDS4501A dosing.
- Subsequent dosing of DCDT2980S/DCDS4501A and rituximab/obinutuzumab is permitted provided that the neutropenia has resolved to Grade $\leq$2 or $\geq$80% of the baseline value, whichever is lower, within the 2-week period.
- If prophylactic G-CSF was not administered prior to the cycle in which the Grade 3–4 neutropenia developed, then prophylactic G-CSF may be administered prior to subsequent cycles without DCDT2980S/DCDS4501A dose reduction. The dose schedule may be changed from 21-day to 28-day cycles to provide sufficient time for neutrophil recovery in subsequent cycles. In the absence of prophylactic G-CSF or dose schedule modification, the dose of DCDT2980S/DCDS4501A in subsequent cycles should be reduced to 1.8 mg/kg *for Arms A and B*. For Cohorts E, G, and H, patients will be given DCDS4501A at a dose of 1.8 mg/kg, and further dose reductions cannot be made.
- If Grade 3–4 neutropenia recurs with prophylactic G-CSF, the dose for subsequent DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg *for Arms A and B*. Prophylactic G-CSF and dose schedule modifications as described above are permitted in order to maintain the reduced DCDT2980S/DCDS4501A dose level and schedule.
- If Grade 3–4 neutropenia recurs at the reduced dose despite the administration of prophylactic G-CSF, then the patient should be discontinued from study treatment.
- For patients enrolled into the non-randomized portion of the study (Cohorts C and D, as well as Cohorts E, G, and H), dose *reductions* will not be allowed *for neutropenia*. Administration of therapeutic/prophylactic G-CSF and dose-schedule modifications as described above are allowed. Patients who have persistent or recurrent Grade 3–4 neutropenia as defined above should be discontinued from study treatment.

The determination of the dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment and with the approval of the Medical Monitor.

4.3.1.7 Peripheral Neuropathy

Peripheral neuropathy (sensory *and/*or motor) is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.3.5). For new or worsening drug-related Grade 2 or 3 peripheral sensory and/or motor neuropathy, dosing should be held for up to 2 weeks until peripheral neuropathy improves to Grade 1 or baseline grade. Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and

approval of the Medical Monitor based on an assessment of the benefit-risk analysis of continuing to delay study treatment.

*For patients enrolled on arms A or B f*ollowing resolution of peripheral neuropathy (sensory and/or motor), subsequent doses of DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg. If worsening Grade 2 or 3 peripheral neuropathy (sensory and/or motor) recurs following dose reduction, study treatment should be discontinued. For Grade *4* peripheral neuropathy (sensory and/or motor), study treatment should be discontinued.

For patients enrolled into *Cohorts C and D,* dose modifications will not be allowed. Patients who have Grade 2 or 3 peripheral neuropathy (sensory and/or motor), as defined above, should be discontinued from study treatment.

For patients enrolled on Cohorts E, G, or H, following resolution of Grade 2 or Grade 3 peripheral neuropathy (sensory and/or motor), subsequent doses of DCDS4501A should be permanently reduced from 1.8 mg/kg to 1.4 mg/kg. If worsening Grade 2 or Grade 3 peripheral neuropathy (sensory and/or motor) recurs following dose reduction, study treatment should be discontinued. For Grade 4 peripheral neuropathy (sensory and/or motor), study treatment should be discontinued.

4.3.1.8 Hyperglycemia

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other ADCs using the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation of improved anti-hyperglycemic medications (see Section 3.4.3.7).

For symptomatic fasting Grade 3 (>250–500 mg/dL) or asymptomatic Grade 4 (>500 mg/dL) hyperglycemia, medical management should be initiated immediately and consultation with a specialist should be considered. If the hyperglycemia persists for >1 week after initiation of management, dose modification, schedule modification, or discontinuation of study treatment should be considered. In these cases, the study Medical Monitor should be consulted to assess the benefit-risk balance of continued study treatment.

4.3.2 Rituximab

4.3.2.1 Formulation

Rituximab (Rituxan®/MabThera®) is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in 500-mg (50-mL) single-use vials. A single-unit, 500-mg carton contains one 50-mL vial of rituximab (10 mg/mL). The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, and 0.7 mg/mL polysorbate 80, after reconstitution with SWFI. The pH is adjusted to 6.5. Vials are for

single use. Each vial and carton will contain a label (either single-panel or booklet) affixed to the vial or carton.

4.3.2.2 Dosage, Administration, and Storage

Rituximab (Rituxan®, MabThera®) will be administered intravenously once per 3-week (or 4-week) cycle. The infusion at 375 mg/m^2 for each dose will be based on the patient's body surface area at screening and will remain the same throughout the study.

If a scheduled dose of rituximab falls outside of the ±2-day window for reasons other than an adverse event, the site must notify and have a discussion with the Genentech Medical Monitor prior to rituximab administration. Such dosing may not necessarily qualify as a protocol deviation, if deemed to be in the best interests of the patient, after consultation with the Medical Monitor and agreed to in advance by the Medical Monitor.

Rituximab should not be administered as an IV push or bolus. Infusion reactions may occur. Premedication consisting of acetaminophen (or paracetamol), diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (e.g., up to 100 mg or an equivalent dose of methylprednisolone) may also be administered beginning with the first infusion, per standard clinical practice. Premedication may attenuate infusion reactions. Because transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

a. First Infusion

The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If infusion reactions do not occur, the infusion rate should be escalated in 50–mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

b. Subsequent Infusions

If the patient tolerates the first infusion well, subsequent rituximab infusions may be administered at an initial rate of 100 mg/hr and increased in 100–mg/hr increments at 30-minute intervals to a maximum of 400 mg/hr, as tolerated. If the patient does not tolerate the first infusion well, the guidelines for the first infusion should be followed.

If a patient tolerates the first three cycles of study treatment without significant infusion reactions, rituximab may be administered as "rapid infusion" in accordance with local institutional guidelines.

c. Storage

Rituximab vials must be stored at 2°C–8°C (36°C–46°F). Rituximab vials should be stored in the outer carton in order to protect them from light. Rituximab solution for

infusion may be stored at 2°C–8°C (36°C–46°F) for 24 hours and has been shown to be stable for an additional 12 hours at room temperature. However, because rituximab does not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between rituximab and PVC or polyethylene (PE) bags have been observed.

See the Rituxan® (Rituximab) Package Insert or SmPC (in the European Union) for additional information.

4.3.2.3 Dosage Modification

There will be no rituximab dose modification in this study. Patients at high risk for TLS complications (see Section 3.4.3.2) may, at the investigator's discretion, receive their initial dose of rituximab over 2 consecutive days (e.g., 125 mg/m^2 on Day 1, 250 mg/m^2 on Day 2; with DCDT2980S/DCDS4501A dose potentially delayed to Day 3).

Any NCI CTCAE (v4.0) toxicity Grade ≥ 3 in severity that is deemed related to rituximab treatment will require interruption of study treatment (both ADC and rituximab) until resolution to Grade ≤ 2 or ≥ 80% of baseline, whichever is lower. Resumption of rituximab treatment may be considered in patients with resolution of toxicities to Grade ≤ 1 within 2 weeks at the discretion of the investigator, after consultation with the Medical Monitor. Failure of such toxicities to resolve after 2-week delay in study treatment will require permanent discontinuation of rituximab. Continuation of rituximab treatment may be permitted on the basis of ongoing clinical benefit following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

If a patient develops unacceptable toxicity to rituximab requiring its discontinuation, single-agent DCDT2980S or DCDS4501A may be continued on the basis of the investigator's assessment of ongoing clinical benefit and with the approval of the Medical Monitor.

4.3.2.4 Schedule Modification

Patients in whom toxicities have not resolved (i.e., to Grade ≤ 1 or ≥ 80% of baseline) may have their study treatment delayed by up to 2 weeks. If after the up to–2-week delay, all study drug–related toxicities have resolved sufficiently, the patient may receive the scheduled doses of rituximab. In addition, a patient's dosing may be changed to a 28-day cycle if it is felt by the investigator and Medical Monitor that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from transient cytopenias without requiring repeated treatment delays.

Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.1). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by

the investigator and approval from the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

4.3.2.5 Infusion Reaction

Patients will be monitored during and after each rituximab infusion for 90 minutes after the first infusion and for 30 minutes after subsequent infusions in the absence of infusion-related adverse events. Patients who experience infusion-related symptoms should be managed as directed in Table 1 (see Section 4.3.1.5).

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction to rituximab, rituximab should be discontinued and no additional rituximab should be administered. Patients who experience these reactions should receive aggressive symptomatic treatment and should be discontinued from study treatment.

4.3.3 Obinutuzumab

4.3.3.1 Formulation

Obinutuzumab (GA101/Gazyva™/Gazyvaro) is a clear, colorless to slightly brownish liquid, provided as a single 1000-mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50–mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188, and highly purified water (HPW).

4.3.3.2 Dosage, Administration, and Storage

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg in combination with DCDS4501A, as outlined in Section 3.1.3. Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–8 (see Table 2). No dose modifications of obinutuzumab are allowed.

All obinutuzumab infusions should be administered after premedication with oral acetaminophen and an antihistamine (see Section 4.4.1). The prophylactic use of corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) may also be considered for patients thought to be at high risk for IRRs, if deemed appropriate by the investigator, and should be administered prior to the obinutuzumab infusion. On Cycle 1 Day 1, it is recommended that oral prednisone, prednisolone, or methylprednisolone be given within 12 hours as a premedication but at least 60 minutes prior to the obinutuzumab infusion. Premedication with prednisone or prednisolone is mandatory in patients who had an IRR and should continue until IRRs no longer occur during antibody infusion. For the management of IRRs and anaphylaxis, see Table 1 (Section 4.3.1.5).

If it is the strong preference of the investigator or of the site (e.g., for logistical reasons) or if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count), the administration of obinutuzumab infusion can be split over 2 days.

Table 2 Administration of First and Subsequent Infusions of Obinutuzumab

First Infusion (Cycle 1 Day 1)	Subsequent Infusions
• Begin infusion at an initial rate of 50 mg/hr. • If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/hour increments every 30 minutes to a maximum of 400 mg/hr. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate used at the time the reaction occurred).	• If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, use full premedication including 100 mg prednisone/prednisolone (until no further IRR occurs), begin infusion at an initial rate of 50 mg/hr, and follow instructions for first infusion. • If the patient tolerated the prior infusion well (defined by absence of Grade 2 reactions during a final infusion rate of ≥100 mg/hr), begin infusion at a rate of 100 mg/hr. • If no reaction occurs, increase the infusion rate in 100-mg/hour increments every 30 minutes, to a maximum of 400 mg/hr. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate used at the time the reaction occurred).

IRR = infusion-related reaction.

In all parts of the study, obinutuzumab must be administered in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available, and patients should be under the close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Table 1 (Section 4.3.1.5).

Obinutuzumab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. Administration sets with PVC, polyurethane (PUR), or PE as a product contact surface and IV bags with polyolefin (PO), polypropylene (PP), PVC, or PE as a product contact surface are compatible and can be used. Do not use an additional in-line filter because of potential adsorption.

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For clinical formulation-specific and batch-specific instructions and information on in-use stability, see the packaging label.

4.3.3.3 Dosage Modification

There will be no obinutuzumab dose modification in this study. Patients at high risk for TLS complications (see Section 3.4.3.2) may, at the investigator's discretion, receive obinutuzumab over 2 consecutive days (with DCDS4501A dose potentially delayed to Day 2 or Day 3).

Any NCI CTCAE (v4.0) toxicity Grade ≥3 in severity that is deemed related to obinutuzumab treatment will require interruption of study treatment (both DCDS4501A and obinutuzumab) until resolution to Grade ≤2 or ≥80% of baseline, whichever is lower. Resumption of obinutuzumab treatment may be considered in patients with resolution of toxicities to Grade ≤1 within 2 weeks at the discretion of the investigator, after consultation with the Medical Monitor. Failure of such toxicities to resolve after 2-week delay in study treatment will require permanent discontinuation of obinutuzumab. Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and approval of the Medical Monitor based on an assessment of the benefit-risk analysis of continuing to delay study treatment.

If a patient develops unacceptable toxicity to obinutuzumab requiring its discontinuation, single-agent DCDS4501A will not be permitted.

4.3.3.4 Schedule Modification

Patients in whom toxicities have not resolved (i.e., to Grade ≤1 or ≥80% of baseline) may have their study treatment delayed by up to 2 weeks. Dosing of both DCDS4501A and obinutuzumab should be held during this period. If all study drug–related toxicities have resolved to Grade ≤*1* or ≥ 80% of baseline, the patient may resume DCDS4501A and obinutuzumab dosing on the regular every–21–day schedule. In addition, a patient's dosing may be changed to a 28-day cycle if it is felt by the investigator and Medical Monitor that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from transient cytopenias without requiring repeated treatment delays.

Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.6). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

Specific guidelines around schedule modifications for thrombocytopenia *and febrile neutropenia* are detailed below in Section 4.3.3.5 *and Section 4.3.3.6*.

4.3.3.5 Thrombocytopenia

Thrombocytopenia is a known risk of obinutuzumab (see Section 3.4.6.4). If the clinical condition of a patient requires the use of concomitant anticoagulants, the patient is at increased risk of bleeding when the platelet count is <20,000/μL. When possible, replace prior therapy with Vitamin K antagonists, such as warfarin, with low-molecular weight heparin (LMWH) or new oral anticoagulants (NOACs) before Cycle 1 Day 1. Clinical decision making may be adjusted depending on the patient-specific assessment of benefit and risk.

In the event of severe thrombocytopenia (platelet count <10,000/μL) and/or symptomatic bleeding (irrespective of platelet count) in patients who are not receiving concomitant anticoagulants or platelet inhibitors:

- Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves. If *Cycle 1 Day 8 is delayed, then skip Day 8 and administer Day 15 as previously scheduled (if thrombocytopenia or symptomatic bleeding has resolved). If Cycle 1 Day 15 is delayed, then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab and DCDS4501A as scheduled (if thrombocytopenia or symptomatic bleeding has resolved).*

In the event of thrombocytopenia with platelet count <20,000/μL and/or symptomatic bleeding (irrespective of platelet count) in patients who are receiving concomitant anticoagulants or platelet inhibitors:

- Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves. *If Cycle 1 Day 8 is delayed, then skip Day 8 and administer Day 15 as previously scheduled (if thrombocytopenia or symptomatic bleeding has resolved). If Cycle 1 Day 15 is delayed, then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab and DCDS4501A as scheduled (if thrombocytopenia or symptomatic bleeding has resolved).*
- For patients who are on LMWH or NOACs, when platelet count <20,000/μL develops, reduce the dose of LMWH or NOACs used.
- For patients who are on platelet inhibitors when thrombocytopenia with platelet count <20,000/μL develops, consideration should be given to temporarily pausing the use of platelet inhibitors.

4.3.3.6 *Febrile Neutropenia*

In the event of febrile neutropenia or neutropenia with infection, hold obinutuzumab until febrile neutropenia or neutropenia with infection resolves.

- *If Cycle 1 Day 8 is delayed long enough that the patient is approaching Day 15, then skip Day 8 and administer Day 15 as previously scheduled (if infection or fever has resolved)*
- *If Cycle 1 Day 15 is delayed long enough that the patient approaching Cycle 2, then skip Day 15 dosing and administer Cycle 2 Day 1 of DCDS4501 as scheduled (if infection or fever has resolved)*
- *Note: Obinutuzumab* Patients will receive DCDT2980S or DCDS4501A at 1.8 mg/kg or 2.4 mg/kg by IV infusion on Day 1 or Day *should not be held for neutropenia without fever or infection*

4.3.4 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (pinatuzumab vedotin [DCDT2980S], polatuzumab vedotin [DCDS4501A], rituximab, and obinutuzumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will be either disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate

documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Concomitant Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by a patient from 7 days prior to the screening evaluation to the end of study visits. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF). Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Concomitant use of hematopoietic growth factors is allowed in accordance with instructions provided in the package inserts.

Patients who experience infusion-related temperature elevations of $>38.5°C$ ($>101.3°F$) or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol ($\geq$ 500 mg) and/or H1 and H2 histamine-receptor antagonists (e.g., diphenhydramine, ranitidine). Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with additional supportive therapies (e.g., supplemental oxygen, β2-agonists, and/or corticosteroids) as clinically indicated according to standard clinical practice (see Table 1).

For patients enrolled on obinutuzumab-containing regimens, it is recommended that *corticosteroids (e.g., 100 mg of IV prednisolone or equivalent)* be given as premedication within 12 hours of, but at least 60 minutes prior to, the obinutuzumab infusion on Cycle 1 Day 1. After the first obinutuzumab infusion, additional glucocorticoids are allowed at the investigator's discretion. For patients who did not experience infusion-related symptoms with their previous infusion, premedication at subsequent infusions may be omitted at the investigator's discretion.

Infusion reaction prophylaxis with medications (e.g., acetaminophen/paracetamol, antihistamines, and/or corticosteroids) may be instituted at any point in the study if it is determined to be in the best interest of the patient on the basis of the observation of IRRs in patients already enrolled in the study. Patients with Grade 3 hypotension or fever must be premedicated prior to retreatment (see Section 4.3.1.5). Patients with hypotension requiring vasopressor support or with Grade 3 wheezing, hypoxia, or generalized urticaria must be permanently discontinued from study treatment.

4.4.2 Excluded Therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy
- Immunotherapy including immunosuppressive therapy
- Radioimmunotherapy
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Biologic agents (other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts); guidelines for the use of G-CSF are detailed in Section 4.3.1.6 and Appendix F.
- Any therapies intended for the treatment of lymphoma or leukemia, whether approved by local regulatory authorities or investigational

Patients who require the use of any of these agents will be discontinued from all study treatment. Patients who are discontinued from study treatment will be followed for safety outcomes for 30 days following the patient's last dose of DCDT2980S or DCDS4501A or rituximab or obinutuzumab, whichever is later, or until the patient receives another anti-cancer therapy, whichever occurs first.

4.5 STUDY ASSESSMENTS

4.5.1 Definitions of Study Assessments

4.5.1.1 Medical History and Demographics

Medical history includes all clinically significant diseases, prior cancer history, prior cancer therapies and procedures, and all medications used by the patient within 7 days preceding the screening visit.

4.5.1.2 Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure while the patient is in a sitting or semi-supine position, pulse oximetry, pulse rate, and body temperature. Every effort will be made to ensure that vital signs are obtained from patients in a consistent manner and position. The timing of vital sign collection on the days of study treatment administration is as follows:

- For the administration of rituximab or obinutuzumab, vital signs should be assessed prior to the start of the infusion, every 15 (±5) minutes during the first hour of the infusion, as clinically indicated during the remainder of the infusion, and following the completion of the infusion.

- For the administration of DCDT2980S or DCDS4501A, vital signs should be assessed prior to the start of the infusion, every 15 (±5) minutes during the infusion, at the end of the infusion, and every 30 (±10) minutes for 90 minutes post-infusion following dosing at Cycle 1 and 30 (±10) minutes following dosing in subsequent cycles.

Additional monitoring of vital signs should be performed if clinically indicated.

4.5.1.3 Physical Examination

A complete physical examination should include the evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Targeted physical examinations should be limited to systems of clinical relevance (i.e., cardiovascular, respiratory, and any system that might be associated with tumor assessment, such as lymph nodes, liver, and spleen) and those systems associated with symptoms.

Changes from baseline should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

Resolution or any change in grade of peripheral neuropathy AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV). This also applies to AEs for which study drug was discontinued or for patients in the follow-up phase after last dose of study treatment with either ongoing AEs or new onset of an AE. For the AEs referring to the follow-up phase newly initiated, relevant treatments need to be documented with treatment dates.

4.5.1.4 Laboratory Assessments

On days of study drug administration, pre-infusion laboratory samples should be drawn within 4 hours prior to the start of infusion, unless otherwise specified. Local laboratory assessments may be obtained up to 72 hours prior to the start of study treatment administration (see below and Section 4.5.3). Instruction manuals and supply kits will be provided for all central laboratory assessments.

Central Laboratory Assessments

Samples for flow cytometry, PK, bone marrow, and anti-DCDT2980S, anti-DCDS4501A, or anti-obinutuzumab antibody assessments will be sent to one or several laboratories or to Genentech for analyses (see Section 3.6). The following assessments will be conducted:

- Leukocyte immunophenotyping/flow cytometry (fluorescence-activated cell sorting [FACS] lymphocyte subsets)

  Whole-blood samples will be collected to analyze B-cell subsets ($CD19^+$), T-cell counts ($CD3^+$, $CD4^+$, $CD8^+$), and NK cell counts ($CD16^+$, $CD56^+$), by flow cytometry.

- ATA assays

  ATAs to DCDT2980S, DCDS4501A, or obinutuzumab will be determined using validated ELISA*s* (see Section 4.9).

- PK and PD assays (see Section 4.5.1.6)
- A plasma sample and blood samples will be collected from patients for exploratory research as indicated in Section 4.5.1.9.
- For patients who sign the optional consent, a blood sample will be collected prior to the first dose of study treatment for exploratory research.
- Tumor tissue sample (archival or fresh) will be collected from patients for central pathologic review as described in Section 4.1.1 and Section 4.5.1.9.

Local Laboratory Assessments

Samples for hematology, serum chemistry, liver function, and pregnancy will be analyzed at the study site's local laboratory. Local laboratory assessments may be obtained up to 72 hours prior to start of study treatment administration on Day 1 of the treatment cycle.

- Hematology: includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells)
- Coagulation: aPTT, PT, and INR
- Quantitative immunoglobulins (IgA, IgG, and IgM)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid*, amylase, and lipase*
- Serum γ-glutamyl transpeptidase (GGT) levels will be required at screening only
- Hemoglobin A1c
- Viral serology and detection (screening assessment only and if clinically indicated)

  Hepatitis B (HBsAg and HBcAb; also HBV DNA by PCR if the patient is HBcAb positive)

  HCV antibody

- Pregnancy test

  For women of childbearing potential (see Section 4.1.2), a serum pregnancy test must be performed within 14 days prior to Cycle 1 Day 1.

  Urine pregnancy tests will be performed during the study treatment period. If any urine test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Any patient with a positive serum test will not be allowed to receive any study treatment.

4.5.1.5 Electrocardiogram Assessments

Twelve-lead digital ECG measurements will be obtained in triplicate, with immediately consecutive ECGs obtained until three evaluable ECGs are recorded, at the following timepoints:

- Screening
- 30–60 minutes before the start of DCDT2980S or DCDS4501A infusion in Cycle 1
- 30–60 minutes after the completion of DCDT2980S or DCDS4501A infusion in Cycle 1
- 30–60 minutes after the completion of DCDT2980S or DCDS4501A infusion in Cycle 3
- Day 8 (±1 day) of Cycle 3 time matched (i.e., obtained at the same time of day) with post-DCDT2980s/DCDS4501A infusion ECGs for Cycle 3
- Treatment completion/early termination visit

Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of or suspicion for clinically significant signs or symptoms of cardiac dysfunction.

All ECGs as described above will be submitted to a Sponsor-designated ECG central laboratory for storage and potential analysis. Detailed instructions on ECG acquisitions and transmissions to the ECG central laboratory will be provided in the ECG manual provided for this study.

Representative ECGs at each timepoint should be reviewed by the investigator or a qualified designee. Post-screening ECG measurements should be obtained as close as possible to scheduled serum and plasma PK samples (see Appendices B-1 and B-2) and should be no more than 30 minutes apart. If QTc prolongation (>500 ms and >60 ms longer than the pre-dose baseline value) is noted, ECGs should be repeated until the prolongation is reversed or stabilized. If a PK sample is not scheduled at the timepoint where QTc prolongation is first observed, then an unscheduled sample should be obtained. An evaluation for potential causes of QT prolongation—for example, electrolyte imbalances or concomitant medications—should be performed, study treatment dosing held, and the Medical Monitor notified. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician.

4.5.1.6 Pharmacokinetic and Pharmacodynamic Assessments

Pharmacokinetics of DCDT2980S and DCDS4501A will be characterized by measuring total antibody (conjugated and unconjugated antibody), acMMAE, and free MMAE concentrations using validated methods (see Section 4.9). Plasma samples may also be analyzed for other potential MMAE-containing catabolites, per sponsor's discretion. Pharmacokinetics of rituximab will be characterized by measuring rituximab concentrations using a validated method (see Section 4.9). Pharmacokinetics of

obinutuzumab will be characterized by measuring obinutuzumab concentrations with use of a validated method (see Section 4.9). These assessments will allow for further characterization of pharmacokinetics of DCDT2980S and DCDS4501A, the assessment of the drug interaction potential when they are given in combination with rituximab or obinutuzumab, and the investigation of potential correlations between PK parameters and safety and/or activity if data allow and at the sponsor's discretion. Pharmacodynamics of obinutuzumab and DCS4501A may be assessed by monitoring the release of tumor associated DNA following treatment.

4.5.1.7 Immunogenicity Assessments

The immunogenicity evaluation will utilize a risk-based strategy and tiered approach (Rosenberg and Worobec 2004a, 2004b, 2005; Koren et al. 2008) designed to detect and characterize all ATA responses to DCDT2980S and DCDS4501A. Patient samples will first be screened to detect all antibody responses toward DCDT2980S or DCDS4501A. Samples that screen positive will be analyzed in a confirmatory assay (competitive binding with DCDT2980S or DCDS4501A) to assess the specificity of the positive response. Titers will be determined for confirmed positive samples. Further characterization will be assessed by competitive binding with the MAb component of DCDT2980S or DCDS4501A to characterize whether the ATA responses are primarily to the mAb or the linker-drug regions of the ADC. Positive ATA samples will be stored for further characterization of ATA responses, if necessary.

The schedule of sample collection for ATA assessment is outlined in Appendices B-1, B-2, or B-3, depending on the schedule of study treatment administration. Samples for ATA will not be collected during the crossover treatment period.

ATA responses to obinutuzumab will be detected and confirmed using a similar tiered approach. Patient samples will first be screened to detect all antibody responses to obinutuzumab. Samples that screen positive will be analyzed in a confirmatory assay (competitive binding with obinutuzumab) to assess the specificity of the positive response. The relative levels of ATA in confirmed positive samples will be determined in a titering assay. Positive ATA samples will be stored for further characterization of ATA responses, if necessary.

4.5.1.8 Tumor Response Assessments

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, on the basis of physical examinations, CT scans, PET scans, and/or MRI scans, and bone marrow examinations, using standard response criteria for NHL (Cheson et al. 2007; *Cheson et al. 2014*) (see Appendix C-1 and C-2).

a. Radiographic Assessments for Patients on Rituximab-Containing Arms/Cohorts

CT scans with contrast should include chest, abdomen, and pelvis scans; CT scans of the neck should be performed at screening and followed only if disease is present at screening. Post-screening radiographic assessments may be limited to areas of prior involvement only if required by local health authorities.

MRI scans may be used instead of CT scans in patients for whom CT scans with IV contrast are contraindicated. Details regarding imaging procedures in these cases will be provided in the Imaging Manual.

An ^{18}F-fluorodeoxyglucose–positron emission tomography (^{18}F-FDG-PET) (hereafter referred to as PET) scan is required during screening for all patients with DLBCL. An additional PET scan in DLBCL patients should be obtained at the 6-month tumor assessment to ensure consistency of response assessment methodology at this timepoint for all patients. PET scans should additionally be obtained to confirm disappearance of metabolically active disease during study treatment and to confirm a CR upon discontinuation of study treatment.

For patients with FL, PET scans are not required but may be obtained on the basis of physician preference and if permitted by local health authorities. Similarly, for DLBCL, PET scans on patients with FL should be obtained during screening; for patients whose tumors are PET positive during screening, an additional PET scan should be obtained at the 6-month tumor assessment. PET scans should additionally be obtained to confirm disappearance of metabolically active disease during study treatment and to confirm a CR upon discontinuation of study treatment.

For all patients regardless of disease subtype, combined PET-CT scans may be used instead of CT alone if performed with contrast and if collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent PET-CT scans. If a PET-CT scan is to be used during screening, then PET-CT scans should be performed for all subsequent tumor assessments in order to ensure their consistency across different timepoints.

All tumor assessments will be submitted to an IRF for storage and possible independent centralized review. Details related to submission of data to the IRF will be defined in a separate Imaging Manual.

b. Radiographic Assessments for Patients on Obinutuzumab-Containing Cohorts

PET scans should minimally extend from skull-base to mid-thigh. Full-body PET scan should be performed when clinically appropriate.

CT scans with oral and IV contrast should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated. CT scans for response

assessment may be limited to areas of prior involvement only if required by local health authorities. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

In patients for whom contrast is contraindicated—for example, patients with contrast allergy or impaired renal CL—CT or combined PET/CT scans without contrast are permitted so long as they permit consistent and precise measurement of target lesions during the study treatment period.

PET and CT scans are required for follicular NHL and DLBCL patients at screening, after Cycle 4 of study treatment (i.e., between Cycle 4 Day 15 and Cycle 5 Day 1), and at EOT. The EOT response assessment should be performed 6–8 weeks after Cycle 8 Day 1 or last study treatment. CT scans without PET scans will be obtained every *6* months for *2* year*s*, with use of *Lugano 2014 R*esponse *C*riteria for NHL (see Appendix C-2).

c. Bone Marrow Assessments

A bone marrow biopsy for morphology is required at screening and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. *For obinutuzumab-containing cohorts, only follicular NHL patients are required to undergo a bone marrow biopsy at screening.* If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated.

d. Schedule of Tumor Response Assessments for Rituximab-Containing Arms/Cohorts

Tumor response assessments will be performed every 3 months (±1 week) from the initiation of study treatment until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). The schedule of tumor assessments is independent of the study treatment dose schedule. For patients enrolled on rituximab-containing arms/cohorts, the schedule of tumor response assessments is detailed in Appendix A-1. As stated above, for all DLBCL patients enrolled on a rituximab-containing arm/cohort, PET scans are required during the screening period and at the 6-month tumor assessment timepoint.

The schedule for tumor response assessments for patients who proceed to crossover treatment is detailed in Appendix A-2.

Additional response assessments, after the final dose of study treatment, for patients who discontinue from study treatment (either initial or crossover treatment) for reasons other than progressive disease, will be performed as described in Appendix A-4.

Tumor assessments should also be performed within 30 days after the last study drug infusion (both initial and crossover treatment) at the treatment completion/early termination visit. Imaging scans are not required at the treatment completion/early termination visit if scans have been performed within the previous 8 weeks or if disease progression while receiving study treatment is documented.

If, at any time during the study, disease progression is suspected, a tumor assessment must be performed.

e. Schedule of Tumor Response Assessments for Obinutuzumab-Containing Cohorts

All follicular NHL and DLBCL patients enrolled in obinutuzumab-containing cohorts are required to have a combined PET and CT scan at screening, after Cycle 4 of treatment, and at EOT. The schedule for tumor response assessments for patients enrolled on obinutuzumab-containing cohorts is detailed in Appendix A-3.

4.5.1.9 Exploratory Research

a. Tumor Tissue Samples

Required Tumor Tissue Samples

Tumor tissue samples will be used for central pathologic laboratory review of CD20, CD22, and CD79b expression. Additional studies to fulfill the exploratory objectives in Section 3.3.4 will be performed, including, but not limited, to the following:

- Messenger RNA (mRNA) expression profiling for signatures of NHL biology, including prognostic subpopulations (Alizadeh et al. 2000; Wright et al. 2003), target expression (CD20, CD22 and CD79b), and apoptotic response
- Tissue microarrays (TMAs) from cores taken from provided blocks for immunohistochemistry (IHC) and in situ hybridization (ISH) assessments for biomarker endpoints involved in response to chemotherapy including quantitation of Bcl-2 protein and genetic alterations of bcl-2 including gene rearrangements, amplifications, and t(14;18) translocations. Additional IHC markers may include those related to the tumor microenvironment.
- Tumor DNA to assess mutations that have been shown to be associated with NHL biology and activation of the B-cell receptor, including mutations in CD79b (Pasqualucci et al. 2011)

For patients who develop progressive disease and are eligible to receive crossover treatment (see Section 3.1.8), a biopsy of a safely accessible site of disease will be performed. Tumor tissue samples obtained at this timepoint will be used to assess changes in biology, target expression, and regulators of apoptosis as described above, which have occurred and may be linked to progression on initial study treatment.

Optional Tumor Tissue Samples (Requires Optional Research Informed Consent

For patients who provide informed consent, an optional tumor biopsy will be collected at time of progression from the following patients:

- Patients who develop disease progression following initial study treatment and do not proceed to receive crossover treatment
- Patients who develop disease progression on crossover treatment

Tumor tissue samples obtained at these timepoints will be used to assess changes in biology, target expression, and regulators of apoptosis, as described above, that have occurred and may be linked to progression on treatment.

b. Blood and Plasma Samples

A plasma sample will be collected prior to treatment.

Blood samples will be taken aligned with PK sampling to assess the pharmacodynamics response by monitoring circulating tumor DNA.

For patients who sign the Optional Research Informed Consent, an additional blood sample will also be taken prior to treatment.

The plasma and blood samples may be used for the assessment of specific tumor biologic markers, including proteins, circulating DNA, and microRNAs. The information obtained from these samples will enable a better understanding of the biology of NHL and disease prognosis, identify potential predictors of response to treatment with DCDT2980S, DCDS4501A, rituximab, and/or obinutuzumab, improve diagnostic assessments, and identify and characterize mechanisms of resistance to DCDT2980S or DCDS4501A and rituximab or obinutuzumab activity.

Because tumorigenesis is a multiple-step process linked to somatic events, any DNA analysis will focus on sporadic mutations specifically found in tumor tissue and not on inherited changes found in the whole body. For this purpose, some tumor-containing sections may be taken from the tissue block and used for the DNA extraction process. Assays on stored tissue samples may be performed at Genentech or at a central specialty laboratory.

4.5.1.10 Patient-Reported Outcomes

The MDASI (Cleeland et al., 2000; Appendix E) is a multi-symptom self-report measure for clinical and research use. The MDASI's 13 core-symptom items, plus an additional 4 items, for a total of 17 symptom items, include those found to have the highest frequency and/or severity in patients with various cancers and treatment types. These include pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and

numbness or tingling. Six additional items focus on the degree of interference of the aforementioned symptoms for a total of 23 items in the questionnaire.

PRO data will be elicited from all patients in this study *(with the exception of Cohorts E, G, and H)* to more fully characterize the clinical profile of study treatment. The MDASI PRO instrument will be supplied in the local language of each participating country. Electronic (handheld computers) will be used for the daily collection of symptoms derived from the MDASI.

4.5.2 Screening and Pretreatment Assessments

All screening evaluations must be completed and reviewed by the Genentech Medical Monitor or designated CRO Medical Monitor to confirm that patients meet all eligibility criteria and are approved for enrollment before the first infusion of study treatment. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site.

Screening and pretreatment tests and evaluations will be performed within 28 days preceding the day of the first dose of study treatment on Cycle 1 Day 1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 may be used; such tests do not need to be repeated for screening.

The availability of a patient's tumor tissue sample for studies (see Section 4.1.1 and Section 4.5.1.9) should be confirmed prior to Cycle 1 Day 1. Such specimens should consist of representative core biopsy in a paraffin block, which is the preferred method, or at least 15 unstained slides. Tumor specimens should be submitted with an accompanying pathology report and may be obtained at any time prior to entry to study.

Bone marrow biopsy and aspirate specimens are required at screening (see Section 4.5.1.8). *For obinutuzumab-containing cohorts, bone marrow biopsy and aspirate are only required for follicular NHL patients*. Unsuccessful attempts at obtaining marrow aspirates will not be considered a protocol deviation or violation.

Refer to the Study Flowchart provided in Appendix A-1 and A-3 for the schedule of screening and pretreatment assessments.

4.5.3 Assessments During Treatment

Study drug infusions (rituximab, obinutuzumab, DCDT2980S, or DCDS4501A) should occur on the scheduled 21-day (or 28-day) cycle but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ±1 day from the scheduled date, unless otherwise noted. Study visits starting in Cycle 3 should occur within ±2 days from the scheduled date, unless otherwise noted.

All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed prior to study drug infusion unless otherwise noted.

Local laboratory assessments may be performed within 72 hours preceding study drug administration on Day 1 of each cycle. Otherwise, laboratory samples should be drawn 0–4 hours before infusion. Results must be reviewed and the review documented prior to study drug administration.

Refer to the Study Flowchart provided in Appendix A-1 for the schedule of treatment period assessments. For patients enrolled in the obinutuzumab-containing cohorts, refer to the Study Flowchart provided in Appendix A-3.

4.5.4 Study Treatment Completion Visit

Patients who complete study treatment or discontinue from study treatment early will be asked to return to the clinic within 30 days after the last DCDT2980S, DCDS4501A, rituximab, or obinutuzumab infusion (whichever is later) for a study treatment completion visit. The visit at which response assessment shows progressive disease may be used as the early termination visit.

Refer to the Study Flowchart provided in Appendix A-1 for assessments to be performed at the treatment completion/early termination visit. For patients enrolled on the obinutuzumab-containing cohorts, refer to the Study Flowchart provided in Appendix A-3.

Assessments conducted at the treatment completion/early termination visit may be used for the purposes of re-screening to determine eligibility to receive crossover treatment (see Section 3.1.3 and Section 4.5.5).

4.5.5 Crossover Treatment Completion Visit

Patients who fulfill the criteria to receive crossover treatment (see Section 3.1.6) will have assessments during the crossover treatment period as described in Appendix A-2. The same guidelines regarding scheduling of assessments for treatment with initial study treatment as detailed in Section 4.5.3 will apply to crossover treatment.

Patients who proceed to receive crossover treatment will have on-treatment assessments as described in Appendix A-2.

Patients who complete the crossover treatment (approximately 1 year/17 cycles) or discontinue from crossover treatment early will be asked to return to the clinic within 30 days after the last DCDT2980S, DCDS4501A, or rituximab infusion (whichever is later) for a crossover treatment completion/early termination visit. The visit at which response assessment shows disease progression on crossover treatment may be used as the early termination visit.

Refer to Appendix A-2 for assessments to be performed at the treatment completion/early termination visit.

4.5.6 Follow-Up Assessments

Ongoing adverse events thought to be related to DCDT2980S, DCS4501A, rituximab, or obinutuzumab will be followed until the event has resolved to baseline (pre-treatment) grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the adverse event.

Patients will be followed after the last dose of study treatment (either initial study treatment or crossover treatment) for safety outcomes. Such follow-up will require an assessment (per verbal report, at minimum) of any adverse events and serious adverse events for 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy, whichever occurs first.

4.5.6.1 Follow-Up Assessments for Rituximab-Containing Regimens

Patients who discontinue from study treatment (either initial study treatment or crossover treatment) for reasons other than progressive disease will be followed for response for up to 1 year after the last infusion of study treatment or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Response assessments should occur approximately every 2–3 months following the last infusions of DCDT2980S, DCDS4501A, or rituximab. Post-treatment assessments are described in Appendix A-4.

Following discontinuation of study treatment, patients will be followed for survival approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination.

4.5.6.2 Follow-Up Assessments for Obinutuzumab-Containing Regimens

Patients who discontinue from study treatment for reasons other than progressive disease will be followed for response for up to 2 years after the last infusion of study treatment or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Response assessments should occur approximately every 2–3 months following the last infusions of DCDS4501A or obinutuzumab for the first year after completion of treatment, then every 6 months for the second year after completion of treatment. Post-treatment assessments are described in Appendix A-5.

Following discontinuation of study treatment, patients will be followed for survival approximately every 6 months until death, loss to follow-up, withdrawal of consent, or study termination.

4.6 PATIENT DISCONTINUATION

4.6.1 Discontinuation from Treatment

Patients may discontinue study treatment early for reasons other than disease progression, such as patient/investigator choice or unacceptable toxicity. The reasons for early discontinuation of treatment must be documented on the appropriate eCRF. Patients may continue treatment with either DCDT2980S/DCDS4501A or rituximab alone following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

Patients who discontinue study treatment early due to toxicity should continue to be followed until resolution of toxicity as scheduled.

Refer to Section 4.5.4 and Section 4.5.5 for assessments that are to be performed for patients who discontinue from the study during the study treatment period.

4.6.2 Discontinuation from Study

Patients must be discontinued from the study if they experience disease progression as defined using response and progression criteria in Appendix C. Patients can continue crossover treatment following documentation of the first progressive disease event but must be discontinued from the study if they experience a second progressive disease event on the crossover treatment.

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study, for reasons of noncompliance (e.g., missed doses or missed visits) or pregnancy or if the investigator determines it is in the best interest of the patient.

Refer to Section 4.5.4 and Section 4.5.5 for assessments that are to be performed for patients who prematurely discontinue from the study during the treatment period.

4.7 STUDY DISCONTINUATION

Genentech has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

4.8 POST-TRIAL ACCESS

Genentech does not have any plans to provide DCDT2980S, DCDS4501A, rituximab, obinutuzumab, or other study interventions to patients after the conclusion of the study or if the study is terminated or for patients who withdraw early from the study or

complete their study treatment. Genentech will evaluate the appropriateness of continuing to provide DCDT2980S, DCDS4501A, rituximab, or obinutuzumab to study patients after evaluating the safety and activity data from the study.

4.9 ASSAY METHODS

4.9.1 Total DCDT2980S/DCDS4501A Antibody ELISA

Total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) will be measured in serum samples using validated ELISAs.

4.9.2 Antibody-Conjugated MMAE (MMAE Affinity Capture Enzyme-Release LC/MS-MS)

acMMAE (a measure of MMAE conjugated to DCDT2980S/DCDS4501A) will be measured in plasma samples using validated affinity capture enzyme-release liquid chromatography–tandem mass spectrometry (LC-MS/MS) assays.

4.9.3 Free MMAE LC-MS/MS

Free MMAE will be measured in plasma samples using a validated electrospray LC-MS/MS method.

4.9.4 Rituximab ELISA

Rituximab will be measured in serum samples using a validated ELISA.

4.9.5 Obinutuzumab ELISA

Obinutuzumab will be measured in serum samples using a validated ELISA.

4.9.6 Anti-Therapeutic Antibody

ATAs against DCDT2980S and DCDS4501A in serum samples will be measured using validated bridging antibody ELISAs and characterized by competitive binding assays.

ATAs against obinutuzumab in serum samples will be measured using a validated bridging antibody ELISA *and characterized by a competitive binding assay*.

4.9.7 Biomarker Assays

Tumor tissue assessment of biomarkers will be assayed using IHC, ISH, qPCR gene expression profiling using microarray and mutation detection assays. Circulating Tumor DNA (ctDNA) in plasma samples may be assessed using a next generation sequencing approach (CAPP-Seq) to detect and quantitate lymphoma specific markers.

4.10 STATISTICAL METHODS

The final analysis will be based on patient data collected until all patients discontinue from the study or the study is terminated by the Sponsor, whichever occurs first. The analyses will be based on the safety evaluable population, defined as patients who

received at least one dose of study treatment. All summaries will be presented according to the disease-specific cohort, treatment group, and assigned dose level.

4.10.1 Analysis of the Conduct of the Study

Enrollment, major protocol violations, and reasons for discontinuations from the study will be summarized.

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, duration of malignancy, and baseline ECOG Performance Status, will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables. All summaries will be presented overall and by treatment group, assigned dose level, and disease-specific cohort.

Study drug administration data will be listed by the disease-specific cohorts described in Section 3.1.1 and Section 3.1.2. Any dose modifications will be flagged. Means and standard deviations will be used to summarize the total doses of DCDT2980S, DCDS4501A, rituximab, and obinutuzumab received. All summaries will be presented by treatment group, assigned dose level, and disease-specific cohort.

4.10.2 Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, and changes in vital signs. All patients who receive any amount of DCDT2980S, DCDS4501A, rituximab, or obinutuzumab will be included in the safety analysis and will be assigned to the treatment group on the basis of the study treatment received. Patients who have dose level changes from the initial assigned dose level will be summarized by the initial assigned dose level of DCDT2980S or DCDS4501A.

All adverse event data will be listed by study site, patient number, treatment group, disease-specific cohort, and cycle. All adverse events occurring on or after treatment on Day 1 of Cycle 1 will be summarized by mapped terms, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade. In addition, all serious adverse events, including deaths will be listed separately and summarized.

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to DCDT2980S and DCDS4501A will be summarized.

4.10.3 Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum concentrations of total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) and rituximab or obinutuzumab and plasma concentrations of acMMAE and free MMAE versus time data will be tabulated and plotted by NHL disease subtype (relapsed or refractory follicular NHL or DLBCL). The pharmacokinetics of the above analytes will be summarized by estimating the appropriate PK parameters (e.g., AUC, C_{max}, CL, V_{ss}, and $t_{1/2}$). Estimates for these

parameters will be tabulated and summarized (mean, standard deviation, and range). Non-compartmental, compartmental, and/or population methods will be used, as data allow.

Exposure-response (safety and efficacy) analysis may be conducted with use of PK data and available drug effect (e.g., imaging, measures of tumor burden) and toxicity (e.g., clinical pathology) data, at the sponsor's discretion.

In addition, population PK methods may be employed to manage sparse data and to investigate the effects of certain covariates on the pharmacokinetics of DCDT2980S and DCDS4501A, as data allow, and at the sponsor's discretion.

4.10.4 Activity Analyses

Best overall response, duration of response, and PFS will be listed for all patients.

ORR from the initial study treatment will be calculated on the basis of data from patients who received study treatment. Objective response is defined as CR or PR as determined by the investigator, on the basis of physical examinations, radiographic scans, and bone marrow examinations, using modified response criteria for NHL (Cheson et al. 2007; see Appendix C) and confirmed by repeat assessments ≥4 weeks after initial documentation. Any patient with insufficient data to determine response will be classified as a non-responder.

For patients with DLBCL, primary assessment of tumor response will be based on diagnostic imaging scans—for example, CT and/or MRI scans and PET scans. For patients with FL enrolled on rituximab-containing arms/cohorts, primary assessment of response will be based on CT scans only; the assessment of response in FL based on PET scans will be performed for exploratory purposes only.

For patients on obinutuzumab-containing cohorts, *primary response assessment for both DLBCL and FL will be* based on PET/CT scans *using the updated 2014 Lugano Response Criteria* as determined by an Independent Review *Committee* (IRC). *P*atients in Cohorts E, G, and H will be evaluated with a PET-CT scan at screening, between Cycle 4 Day 15 and Cycle 5 Day 1, and at *the end of treatment (*6-8 weeks after completing treatment*)*. The efficacy analysis for these cohorts will, therefore, be different from the analysis for Arms A-B and Cohorts C-D (Cheson, et al 2014) (see Appendix C-2). *Subsequent imaging can be CT only. Responses to study treatment will also be based on investigator assessments.*

Among patients with an objective response, duration of response will be defined as the time from the initial documentation of a CR or PR to the time of disease progression or death. If a patient does not experience death or disease progression before the end of the study, duration of response will be censored at the day of the last tumor assessment.

For the randomized portion of the study (Arms A and B), PFS is defined as the time from the date of randomization to the date of disease progression or death from any cause, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the date of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. For the non-randomized portion of the study (Cohorts C through H), PFS is defined as the time from the date of study enrollment to the date of disease progression or death from any cause, whichever occurs first.

For the randomized portion of the study (Arms A and B), OS is defined as the time from the date of randomization to the date of death from any cause. For the non-randomized portion of the study (Cohorts C through H), OS is defined as the time from the date of study enrollment to date of death from any cause.

4.10.5 Exploratory Analyses

Assay results of possible predictive markers will be listed by treatment group and response status.

Frequencies and percentages of missing data for the PRO endpoints will be reported. Dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) will be summarized

Summary statistics of the MDASI items, scales, and their changes from baseline will be calculated at each assessment timepoint. The mean, standard error, and median of the absolute scores and the mean changes from baseline (and 95% CI) within and between study arms will be reported for the MDASI scales and single items, as well as the weekly averages of the worst symptom rating. For change scores in the MDASI from baseline, patients without baseline scores will not be included in the analyses. Line charts depicting the means and mean changes of subscales over time will be also provided.

Repeated measures mixed-effects models will explore MDASI subscale scores with a baseline score and appropriate covariates added, as appropriate.

4.10.6 Handling of Missing Data

For the endpoint of objective response, patients without a post-baseline tumor assessment will be considered non-responders in the all-treated population analysis.

For duration of response and PFS, data from patients who are lost to follow-up will be included in the analysis as censored observations on the last date that the patient is known to be progression free, defined as the date of the last tumor assessment, or, if no tumor assessments were performed, as the date of last study treatment plus 1 day.

Compliance to PRO data collection will be reported with summary statistics, including frequencies of reasons for non-compliance such as patient refusal to complete PRO data collection.

4.10.7 Determination of Sample Size

For the randomized portion of the study (Arms A and B), a target of 120 patients will be enrolled in two separate cohorts of patients (40 in the follicular NHL cohort and 80 in the DLBCL cohort). The randomized portion of this study is non-comparative in nature. No formal hypothesis testing is planned to compare the treatment arms. Moreover, there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms. Genentech has judged the proposed sample size to provide sufficient precision in estimating the anti-tumor activity of DCDT2980S combined with rituximab or DCDS4501A combined with rituximab as measured by objective response. For example, with the assumption of an observed response rate of 40%, a 90% confidence interval for the response rate would be approximately 22%–58% (i.e., 40% ± 18%) for the follicular NHL cohort and approximately 27%–53% (i.e., 40% ± 13%) for the DLBCL cohort. With 40 patients, there is an 87% chance of observing at least one adverse event with a true incidence of 5%.

For the non-randomized portions of the study (Cohorts C and D), approximately 20 patients will be enrolled into each arm, for a total of 40 patients. With 20 patients under an observed response rate of 40%, the exact Clopper-Pearson 90% confidence interval for the response rate would be 22%–61%. With respect to the assessment of safety based upon a sample size of 20 patients, the chance of observing at least one adverse event with a true incidence of 10% is 88%.

For the obinutuzumab safety run-in cohort (Cohort E), 6 patients will be enrolled. For the obinutuzumab expansion cohorts (Cohorts G and H), 40 patients with follicular NHL, and 40 patients with DLBCL will be enrolled at the RP2D to further evaluate safety and efficacy of the combination. Table 3 provides asymptotic 90% confidence intervals for the true probability of response for a range of observed proportions based upon a sample of 40 patients. A sample size of 40 patients is deemed sufficient to provide adequate precision on the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting rate of 45% assuming observed response rates of approximately 60% or higher (~24 responders observed among 40 patients).

Table 3 Potential 90% Interval Estimates for the True Response Probability

Observed Proportion of Responders	90% Confidence Interval for True Probability of Response
0.50	(0.37, 0.63)
0.60	(0.47, 0.73)
0.65	(0.53, 0.77)
0.70	(0.58, 0.82)
0.75	(0.64, 0.86)

Therefore, up to 2*46* patients may be enrolled in this study.

4.11 DATA QUALITY ASSURANCE

The data will be collected via EDC using eCRFs. The site will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The CRO will be responsible for the data management of this trial, including quality checking of the data.

Genentech will perform oversight of the data management of this trial. Genentech will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central Laboratory data and other electronic data will be sent directly to Genentech, using Genentech's standard procedures to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Genentech and records retention for the study data will be consistent with Genentech's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and physical examinations and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

Genentech or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Genentech or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Genentech or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central Institutional Review Board/ethics committee (IRBs/ECs, except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

5.1.1 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the baseline hematologic malignancy (i.e., leukemia or lymphoma) that were not present prior to the AE reporting period (see Section 5.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., medication washout, no treatment run-in, or invasive procedures such as biopsies)
- Preexisting medical conditions other than the disease under study that are judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

5.1.2 Serious Adverse Event

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the investigator (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). “Serious” is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

5.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions), irrespective of regulatory seriousness criteria. Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy’s law (see Section 5.3.1.6; treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN [of which $\geq 35\%$ is direct bilirubin])
- Suspected transmission of an infectious agent by the study drug*, as defined below:*

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- *Tumor lysis syndrome (TLS) of any grade, irrespective of causality*

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 5.1) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

5.2.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

After initiation of study drug (the Genentech product(s) or other IMP), all new AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see Section 5.6).

5.2.2 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation timepoints should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.2.3 Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity, and causality.

Table 4 provides guidance for grading AE severity, and Table 5 provides guidance for assessing the causal relationship to the investigational product(s).

The AE grading (severity) scale found in the NCI CTCAE v4.0 will be used for AE reporting.

Table 4 Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Transient or mild discomfort (<48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

AE=adverse event; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; SAE=serious adverse event.

The NCI CTCAE v4.0 can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE (see Section 5.1.2).

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.

To ensure consistency of causality assessments, investigators should apply the following general guidelines:

Table 5 Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

AE=adverse event; SAE=serious adverse event.

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

5.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

5.3.1 Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF. Avoid colloquialisms and abbreviations.

There is one eCRF page for recording AEs or SAEs.

Only one medical concept should be recorded in the event field on the Adverse Event eCRF.

5.3.1.1 Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

5.3.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

5.3.1.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation timepoints. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation timepoints and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF.

5.3.1.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management, e.g., concomitant medication, will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.)

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Specific to this study, lymphopenia and leukopenia due to lymphopenia of any grade are expected PD effects of study drug and therefore are not considered to be AEs. However, complications of lymphopenia (e.g., infections) will need to be reported as AEs. In addition, because monocytopenia is not reportable and neutropenia is already being monitored and reported as an AE, leukopenia does not need to be reported as a distinct AE.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

5.3.1.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (including a diagnostic evaluation not mandated in this protocol) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.1.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or a non-serious adverse event of special interest (see Section 5.4.2)

5.3.1.7 Deaths

Deaths that occur during the protocol-specified AE reporting period (see Section 5.2.1) that are attributed by the investigator solely to progression of lymphoma will be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of attribution, will be recorded on the Adverse Event eCRF and expeditiously reported to the Sponsor.

When recording a death on an eCRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” on the Adverse Event eCRF.

5.3.1.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History eCRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.1.9 Worsening of Baseline Hematologic Malignancy

Worsening and/or progression of the baseline hematologic malignancy (e.g. leukemia or lymphoma) should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

5.3.1.10 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

5.3.1.11 Pregnancy

If a female patient becomes pregnant while receiving the study drug or within 12 months after the last dose of study treatment, a Pregnancy Report eCRF should be completed within 24 hours of learning of the pregnancy. A pregnancy report will automatically be generated and sent to Genentech's Drug Safety Department or its designee. Pregnancy should not be recorded on the Adverse Event eCRF.

Male patients must also be instructed to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the last dose of study drug. If such an event occurs, it should be reported as described below.

Abortion, whether therapeutic or spontaneous, should always be classified as an SAE (as the Sponsor considers these medically significant), recorded on an Adverse Event eCRF, and expeditiously reported to the Sponsor (see Section 5.4.2).

Any congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and expeditiously reported to the Sponsor (see Section 5.4.2).

After the study period, abortions, congenital anomalies/birth defects, and pregnancy outcomes should still be reported expeditiously to the Sponsor.

In the event the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee within 24 hours of learning of the pregnancy, at the fax numbers listed in Section 5.4.2.

a. Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 1 working day after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee within 24 hours of learning of the pregnancy, at the fax numbers listed in Section 5.4.2.

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

5.4.1 Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an eCRF within 24 hours as described in Section 5.4.2.

Medical Monitor Contact Information for sites in North America:

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

For sites outside of North America, local contact details and numbers for safety issues and safety reporting will be provided in the study reference binder.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of SAEs and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the EDC system. A report will be

generated and sent to the Sponsor's Safety Risk Management department by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Sites in North America:

Fax No.: [redacted]

Sites in Europe:

Fax No.: [redacted]

Relevant follow-up information should be submitted to Genentech's Drug Safety Department or its designee as soon as it becomes available and/or upon request.

5.5 TYPE AND DURATION OF FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV).

For some SAEs, the Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

5.6 POST-STUDY ADVERSE EVENTS

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt to be related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to Genentech Drug Safety on the study eCRF. If the study eCRF is no longer available, the investigator should report the event directly

to Genentech Drug Safety either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided below.

Canada:

Fax No.: (905) 542–5864

Email: mississauga.drug_safety@roche.com

France:

Fax No: 33 147617777

Email: neuilly.drug_safety@roche.com

Germany:

Fax No.: [redacted]

Email: grenzach.drug_safety@roche.com

Italy:

Fax No.: [redacted]

Email: monza.drug_safety@roche.com

Netherlands:

Fax No.: [redacted]

Email: woerden.drug_safety@roche.com

United States:

Fax No.: [redacted]

Email: us_drug.safety@gene.com

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with Genentech or a Genentech representative:

- FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

  The names of any subinvestigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.

- Current curricula vitae and evidence of licensure of the Principal Investigator and all subinvestigators

- Complete financial disclosure forms for the Principal Investigator and all subinvestigators listed on the FDA Form 1572
- Federalwide Assurance number or IRB statement of compliance
- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form

  Genentech or its designee must review any proposed deviations from the sample Informed Consent Form.
- Current laboratory certification of the laboratory performing the analysis (if other than a Genentech-approved central laboratory), as well as current references ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator Brochure Receipt signed and dated by the Principal Investigator
- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable) , IRB/EC approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator
- Canada only when applicable: original Qualified Investigator Undertaking Form, signed by each Canadian investigator involved in the study
- For global studies, list documents as appropriate for additional countries.

6.2 STUDY COMPLETION

The following data and materials are required by Genentech before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- All laboratory certifications for laboratories performing the analysis (is other than Genentech-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and subinvestigator, FDA Form 1572 for each site)

- A signed and dated Protocol Amendment Acceptance Form(s) [if applicable]
- Updated financial disclosure forms for the Principal Investigator and all subinvestigators listed on the FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

6.3 INFORMED CONSENT FORM

Genentech's Sample Informed Consent Form will be provided to each site. Genentech or its designee must review and approve any proposed deviations from the Sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the Consent Forms during their participation in the study. The final IRB/EC-approved Consent Forms must be provided to Genentech for regulatory purposes.

The Consent Forms must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved Informed Consent Form must be provided to Genentech for regulatory purposes.

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval, and other processes outlined above apply except that IRB/IEC review and approval may not be required per study site policies.

Optional Research Informed Consent

Informed consent for the collection and use of fresh tumor tissue at time of progression for optional research described in Section 4.5.1.10 will be documented in a section of the main Informed Consent Form. This section provides patients with the option to authorize

the collection and use of these samples and personal health information for additional research purposes. Agreement to participate in the optional research (by checking the appropriate box in this section of the main Informed Consent Form) is not required for enrollment in the trial but is required prior to any optional research sample collection. Optional consent may be withdrawn at any time by the patient.

6.4 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from Genentech. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's Study File.

6.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Genentech representative to inspect site facilities and equipment, study source data, patients' medical records, and eCRFs. The Principal Investigator will oversee all aspects of the conduct of this protocol and permit Genentech monitors/representatives and collaborators, the FDA, other regulatory agencies, Institutional Review Boards, and the respective national or local health authorities to inspect facilities and records relevant to this study.

6.6 ELECTRONIC CASE REPORT FORMS

eCRFS are to be completed using the [redacted] EDC system. Sites will receive training for appropriate eCRF completion. eCRFs will be submitted electronically to Genentech and should be handled in accordance with instructions from Genentech.

All eCRFs should be completed by designated, trained personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

In addition, at the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

6.7 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing SDV to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where original patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, certified accurate and complete copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Original source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to all applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

6.8 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

In collaboration with the study monitor, Genentech's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

6.9 STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by Genentech. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Genentech with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

6.10 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

6.11 RETENTION OF RECORDS

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of Genentech. Written notification should be provided to Genentech prior to transferring any records to another party or moving them to another location.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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Appendix A-1
Study Flowchart: Initial Study Treatment (Arms A-B, Cohorts C-D)

Cycle	Screening	Treatment Period											Treatment Completion/Early Termination Visit [c]	Safety and Survival Follow-Up [d]
		Cycle 1				Cycles 2–4				Cycles 5–17				
Day(s)[a] Assessment	–28 to –1	1 [b]	2	8	15	1 [b]	2	8	15	1 [b]	2	15		
Written informed consent [e]	x													
Review inclusion/exclusion criteria	x													
Medical history and demographics	x													
Height (screening only) and weight	x	x				x				x				
Vital signs	x	x [f]	x [f]	x	x	x [f]	(x) [f]	x	x	x [f]	(x) [f]	x	x	
ECOG Performance Status	x	x		x	x	x		x	x	x			x	
B symptoms [g]	x	x				x				x			x	
Complete physical examination [h]	x													
Targeted physical examination [i]		x	x	x		x	(x)			x	(x)		x	
Concomitant medications	x	x	x	x	x	x	(x)	x	x	x	(x)	x	x	
Adverse events [j]	x	x	x	x	x	x	(x)	x	x	x	(x)	x	x	x
MDASI PRO [k]		Day 1–8 of Cycles 1–8												
12-lead electrocardiogram [l]	x	Refer to Footnote “l”											x	
Tumor assessments [m]	x	Every 3 months											x	
PET scan (required for DLBCL; optional for FL) [m]	x	6-month tumor assessment and as clinically indicated												
Rituximab infusion		x				x				x				
DCDT2980S or DCDS4501A infusion [n]			x			x	(x)			x	(x)			

Appendix A-1 (cont.)
Study Flowchart: Initial Study Treatment (Arms A-B, Cohorts C-D)

Cycle	Screening	Treatment Period											Treatment Completion/Early Termination Visit [c]	Safety and Survival Follow-Up [d]
		Cycle 1				Cycles 2–4				Cycles 5–17				
Day(s)[a]														
Assessment	–28 to –1	1 [b]	2	8	15	1 [b]	2	8	15	1 [b]	2	15		
Local Laboratory Assessments														
HBV and HCV screening [o]	x													
Hematology [p]	x	x		x	x	x		x	x	x		x	x	
Serum chemistry [q]	x	x		x	x	x		x	x	x		x	x	
Hemoglobin A1c	x									Cycle 5 Day 1				
Total IgA, IgG, IgM	x									Cycle 8 Day 1			x	
Coagulation (aPTT, PT, and INR)	x													
Pregnancy test [r]	x	Within 10 days of Day 1 of Cycles 3, 6, 9, 12, and 15											x	
Bone marrow biopsy [s]	x	Perform to confirm CR if positive for disease at screening or if clinically indicated												
Central Laboratory Assessments														
Leukocyte immunophenotyping (FACS) [t]		Day 1 of Cycle1, Cycle 4, Cycle 8 and Cycle12											x	
Tumor tissue sample [u]	x												x	
Exploratory plasma (required) and blood (optional) sample [v]	x													
DCDT2980S or DCDS4501A and rituximab pharmacokinetic sampling [w]	Refer to Appendix B-1 and Appendix B-2													
Serum sample for anti-DCDT2980S or anti-DCDS4501A antibody [x]														

Appendix A-1 (cont.)
Study Flowchart: Initial Study Treatment (Arms A-B, Cohorts C-D)

AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CR = completed response; CT = computed tomography; DLBCL = ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; FL = follicular lymphoma; GGT = γ-glutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; MDASI = MD Anderson Symptom Inventory; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography; PCR = polymerase chain reaction; PT = prothrombin time; QLQ = Quality of Life Questionnaire; SAE = serious adverse event; (x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle —refer to footnote 'n' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 1 year (approximately 17 cycles on an every-21-day schedule) and may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ±1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 3 should occur within ±2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DCDT2980S or DSDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 1 year of total study treatment (approximately 13 cycles).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding rituximab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] Perform within 30 days after the last infusion of DCDT2980S, DCDS4501A, or rituximab. The visit at which response assessment shows progressive disease may be used as the early termination visit. Assessments during the treatment completion/early termination visit may be applied to assessments required to determine eligibility to receive crossover treatment. Patients enrolled into Cohorts C and D are not eligible to receive crossover treatment.

[d] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report from the patient, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-4 for schedule of assessments during the post-treatment period. Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

[e] Informed consent form(s) must be signed by the patient before any study-specific procedures are performed.

[f] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2 of the protocol.

[g] Defined as unexplained weight loss >10% over previous 6 months, fever (>38°C/100.4°F), and/or drenching night sweats.

[h] Complete physical examination includes all systems described in Section 4.5.1.3.

[i] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDT2980S or DCDS4501A dosing on Day 2 of each cycle if given on separate days from rituximab only if clinically indicated—for example, to follow- up on signs or symptoms observed from the examinations performed on Day 1.

[j] After informed consent is obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs and SAEs, regardless of attribution, must be reported until 30 days following the last administration of study drug or until the patient receives another anti-cancer therapy, whichever occurs first. After this period, investigators should report only SAEs considered related to prior study treatment.

[k] Treatment and disease associated symptoms using the MDASI questionnaire will be collected on hand-held computer devices (see Section 4.5.1.10).

[l] Twelve-lead digital electrocardiogram (ECG) measurements must be obtained in triplicate (with immediately consecutive ECGs obtained until three evaluable ECGs are recorded) at the timepoints specified in Section 4.5.1.5. Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction. The evaluating physician should determine the clinical significance of any abnormal ECGs.

[m] Tumor assessments should be performed at screening and every 3 months while receiving study treatment regardless of study treatment dose schedule. Tumor assessments should also be performed within 30 days after the last study drug infusion as part of the treatment completion/early termination visit. Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C-1). For DLBCL patients, a PET scan is required during screening, at the 6-month tumor assessment timepoint and as clinically indicated. For patients with FL, a PET scan is not required but may be obtained based on physician preference and if permitted by local health authorities. Refer to Section 4.5.1.8 for complete details.

[n] Administer DCDT2980S or DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related AEs. For Cycle 1 and Cycle 2, DCDT2980S or DCDS4501A should be administered on the day after rituximab is administered—for example, Day 2 if rituximab is given on Day 1, or Day 3 if rituximab is given as a split dose on Days 1 and 2. In the absence of any infusion-related AEs, rituximab followed by DCDT2980S or DCDS4501A may be administered on the same day in each cycle starting with Cycle 3. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[o] HBsAg, HBcAb, and Hep C Ab serology required. If HBcAb or HCV antibody is positive, HBV/HCV DNA by PCR is required.

[p] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[q] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid. Serum GGT levels will be required at screening only.

[r] A serum pregnancy test should be performed for women of childbearing potential within 14 days prior to receiving first study treatment. In addition, a urine pregnancy test must also be performed within 10 days prior to Day 1 of Cycles 3, 6, 9, 12, and 15, and at the treatment completion/early termination visit unless patient receives crossover treatment, in which case follow the schedule of pregnancy testing outlined in Appendix A-2. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[s] Bone marrow biopsy for morphology (aspirates for morphology and/or flow studies are optional) is required at screening. Bone marrow biopsy for morphology is required at screening and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate

presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated. Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.

[t] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[u] Availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, obtained at any time prior to entry to study. A biopsy of a safely accessible site of disease, defined as requiring only local anesthesia and in general excluding brain, lungs or any internal organs that may subject patients to significant risk, is required for patients who proceed to crossover treatment; if no such lesion exists, then a biopsy is not required.

[v] All patients who have successfully passed screening and are fully eligible for the study will have a 10-mL plasma sample taken for exploratory research.

[w] Pharmacokinetic serum and plasma samples should be drawn according to the schedule provided in Appendices B-1 and B-2.

[x] Whole blood samples for assessment of anti-DCDT2980S or anti-DCDS4501A antibodies in serum will be drawn according to the schedule provided in Appendices B-1 and B-2.

Appendix A-2
Study Flowchart: Crossover Treatment (Patients Randomized to Arms A or B Only)

Cycle	Treatment Period											Crossover Treatment Completion/Early Termination Visit [c]	Safety and Survival Follow-Up [d]
	Cycle 1b				Cycles 2b–4b				Cycles 5b–17b				
Day(s) [a] Assessment	1 [b]	2	8	15	1 [b]	2	8	15	1 [b]	2	15		
Weight	x				x				x				
Vital signs	x [e]	(x) [e]	x	x	x [e]	(x) [e]	x	x	x [e]	(x) [e]	x	x	
ECOG Performance Status	x		x	x	x		x	x	x			x	
B symptoms [f]	x				x				x			x	
Targeted physical examination [g]	x	(x)	x		x	(x)			x	(x)		x	
Concomitant medications	x	(x)	x	x	x	(x)	x	x	x	(x)	x	x	
Adverse events [h]	x	(x)	x	x	x	(x)	x	x	x	(x)	x	x	x
Tumor assessments [i]	Every 3 months											x	
Rituximab infusion	x				x				x				
DCDT2980S or DCDS4501A infusion [j]	x	(x)			x	(x)			x	(x)			
Local Laboratory Assessments													
Hematology [k]	x		x	x	x		x	x	x		x	x	
Serum chemistry [l]	x		x	x	x		x	x	x		x	x	
Total IgA, IgG, IgM									Cycle 8b Day 1			x	
Pregnancy test [m]	Day 1 of Cycles 3b, 6b, 9b, 12b, and 15b											x	
Bone marrow biopsy [n]	Perform to confirm CR if positive for disease at screening or if clinically indicated												
Central Laboratory Assessments													
Leukocyte immunophenotyping (FACS) [o]	Day 1 of Cycle 4, 8, and 12											x	
Tumor biopsy/sample												x [p]	

Appendix A-2 (cont.)
Study Flowchart: Crossover Treatment (Patients Randomized to Arms A or B Only)

AE = adverse event; AL = alanine aminotransferase; AST = aspartate aminotransferase; CR = complete response; LDH = lactate dehydrogenase; SAE = serious adverse event; (x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle—refer to footnote 'j' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 1 year (approximately 17 cycles) and may be given up to ± 2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ± 1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 3 should occur within ± 2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DCDT2980S or DSDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 1 year of total study treatment (approximately 13 cycles).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding rituximab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] Perform within 30 days after the last infusion of DCDT2980S, DCDS4501A or rituximab. The visit at which response assessment shows progressive disease may be used as the early termination visit.

[d] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-4 for schedule of assessments during the post-treatment period. Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

[e] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2 of the protocol.

[f] Defined as unexplained weight loss > 10% over previous 6 months, fever (> 38°C/100.4°F), and/or drenching night sweats.

[g] Targeted physical examinations should be limited to systems of clinical relevance and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDT2980S or DCDS4501A dosing on Day 2 of each cycle if given on separate days from rituximab only if clinically indicated, e.g. to follow -up on signs or symptoms observed from the examinations performed on Day 1.

[h] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-4 for schedule of assessments during the post-treatment period.

[i] Tumor assessments should be performed at screening and every 3 months while receiving study treatment. Tumor assessments should also be

performed 28–56 days after the last study drug infusion as part of the crossover treatment completion/early termination visit. Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C-1).

[j] Administer DCDT2980S or DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related adverse events. For Cycle 1b and Cycle 2b, DCDT2980S or DCDS4501A should be administered on the day after rituximab is administered, e.g., Day 2 if rituximab is given on Day 1, or Day 3 if rituximab is given as a split dose on Days 1 and 2. In the absence of any infusion-related adverse events, rituximab followed by DCDT2980S or DCDS4501A may be administered on the same day in subsequent cycles starting with Cycle 3b. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle, but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[k] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[l] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT), AST, alkaline phosphatase, LDH, and uric acid.

[m] A serum pregnancy test should be performed for women of childbearing potential within 14 days prior to receiving first study treatment. In addition, a serum or urine pregnancy test must be performed within 10 days prior to Day 1 of Cycles 3, 6, 9, 12, and 15 and at the crossover treatment completion/early termination visit. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[n] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[o] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[p] Optional tumor biopsy of a safely accessible site of disease, defined as requiring only local anesthesia and in general excluding brain, lungs or any internal organs that may subject patients to significant risk. Tumor samples will be used for research purposes.

Appendix A-3
Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H): Initial Study Treatment

Cycle	Screening	Treatment Period									Treatment Completion/ Early Termination Visit[c]	End of Treatment Response Assessment (after Cycle 8 Day 1 or last study treatment +6–8 weeks)	Safety and Survival Follow-Up [d]
		Cycle 1				Cycles 2–4		Cycle 4	Cycles 5–8				
Day(s)[a] Assessment	–28 to –1	1[b]	2	8	15	1[b]	2	15[c]	1[b]	2			
Written informed consent[e]	x												
Review inclusion/exclusion criteria	x												
Medical history and demographics	x												
Height (screening only) and weight	x	x				x			x				
Vital signs	x	x[f]	x[f]	x[f]	x[f]	x[f]	(x)[f]		x[f]	(x)[f]	x		
ECOG Performance Status	x	x		x	x	x			x		x		
Complete physical examination *g*	x												
Targeted physical examination *h*		x	x	x		x	(x)		x	(x)	x		
Concomitant medications	x	x	x	x	x	x	(x)		x	(x)	x		
Adverse events *i*	x	x	x	x	x	x	(x)		x	(x)	x		x
12-lead electrocardiogram *j*	x	Refer to Footnote "*j*"									x		
Tumor/Assessment (PET/CT scan (required for DLBCL and FL) *k*	x							x[m]				x[m]	

Appendix A-3 (cont.)

Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H): Initial Study Treatment

Obinutuzumab infusion		x		x	x	x			x				
DCDS4501A infusion [l]			x			x	(x)		x	(x)			
Local Laboratory Assessments													
HBV and HCV screening [m]	x												
Hematology [n]	x	x		x	x	x			x		x		
Serum chemistry [p]	x	x		x	x	x			x		x		
Hemoglobin A1c	x								Cycle 5 Day 1				
Total IgA, IgG, IgM	x								Cycle 8 Day 1		x		
Coagulation (aPTT, PT, and INR)	x												
Pregnancy test [p]	x	Within 10 days of Day 1 of Cycles 3, 6									x		
Bone marrow biopsy [q]	x[q]	Perform to confirm CR if positive for disease at screening or if clinically indicated											
Central Laboratory Assessments													
Leukocyte immunophenotyping (FACS) [t]		Day 1 of Cycle1, Cycle 4, and Cycle 8									x		
Tumor tissue sample [u]	x										x		
Exploratory plasma sample [v]	x												
DCDS4501A and obinutuzumab pharmacokinetic sampling[w]	Refer to Appendix B-3												
Serum sample for anti-DCDS4501A antibody[x]	Refer to Appendix B-3												

Appendix A-3 (cont.)

Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H): Initial Study Treatment

AE = adverse event; ALP = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CR = completed response; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; FLL = follicular lymphoma; GGT = γ-glutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactase dehydrogenase; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography; PT = prothrombin time; SAE = serious adverse event; (x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle—refer to footnote 'n' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 6 months (8 cycles on an every-21-day schedule) and may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycle 1 must occur within ±1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 2 should occur within ±2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DCDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 6 months of total study treatment (6 cycles on an every-28-day schedule).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding obinutuzumab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] Cycle 4 Day 15 assessment should be performed between Cycle 4 Day 15 and Cycle 5 Day 1. The Treatment Completion/Early Termination Visit should be performed within 30 days after the last infusion of DCDS4501A or obinutuzumab. The visit at which response assessment shows progressive disease may be used as the early termination visit.

[d] Patients will be followed for safety for 30 days after the last infusions of DCDS4501A or obinutuzumab. Such follow-up will require an assessment (per verbal report from the patient, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 2 years after the last infusions of DCDS4501A or obinutuzumab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-5 for schedule of assessments during the post-treatment period. Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

[e] Informed consent form(s) must be signed by the patient before any study-specific procedures are performed.

[f] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2of the protocol.

[g] Complete physical examination includes all systems described in Section 4.5.1.3.

[h] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDS4501A dosing on Day 2 of each cycle if given on separate days from obinutuzumab only if clinically indicated (e.g., to follow up on signs or symptoms observed from the examinations performed on Day 1).

[i] After informed consent is obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs and SAEs, regardless of attribution, must be reported until 30 days following the last administration of study drug or until the patient receives another anti-cancer therapy, whichever occurs first. After this period, investigators should report only SAEs considered related to prior study treatment.

[j] Twelve-lead digital electrocardiogram (ECG) measurements must be obtained in triplicate (with immediately consecutive ECGs obtained until three evaluable ECGs are recorded) at the timepoints specified in Section 4.5.1.5. Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction. The evaluating physician should determine the clinical significance of any abnormal ECGs.

Appendix A-3 (cont.)

Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H): Initial Study Treatment

[k] Response *assessment should be performed* using *Lugano Response C*riteria (Appendix C-2). For DLBCL and FL patients, a combined PET/CT scan is required during screening, between Cycle 4 Day 15 and Cycle 5 Day 1, End of Treatment (EOT) assessment, and as clinically indicated. The EOT assessment should be performed 6–8 weeks after Cycle 8 Day 1 or last study treatment. During the follow-up period, *scans (CT or PET/CT) should be performed every 6 months for 2 years or until study end or at any time that progression is suspected.* Refer to Appendix A-5 for imaging assessment during post-treatment follow-up. Refer to Section 4.5.1.8 for complete details for radiographic assessments.

[l] Administer DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related adverse events. For Cycle 1, DCDS4501A should be administered on the day after obinutuzumab is administered (e.g., Day 2 if obinutuzumab is given on Day 1, or Day 3 if obinutuzumab is given as a split dose on Days 1 and 2). In the absence of any infusion-related adverse events, obinutuzumab followed by DCDS4501A may be administered on the same day in each cycle starting with Cycle 2. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[m] HBsAg, HBcAb, and Hep C Ab serology required. If HBcAb or HCV antibody is positive, HBV/HCV DNA by PCR is required.

[n] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[o] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid*., amylase, and lipase* Serum GGT levels will be required at screening only.

[p] A serum pregnancy test should be performed for women of childbearing potential within 14 days prior to receiving first study treatment. In addition, a urine pregnancy test must also be performed within 10 days prior to Day 1 of Cycles 3, and 6 and at the treatment completion/early termination visit. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[q] Bone marrow biopsy for morphology (aspirates for morphology and/or flow studies are optional) is required at screening *for follicular NHL patients only* and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated. Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.

[r] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[s] Availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, obtained at any time prior to entry to study.

[t] All patients who have successfully passed screening and are fully eligible for the study will have a 10-mL plasma sample taken for exploratory research prior to receiving study treatment.

[u] Pharmacokinetic serum and plasma samples and pharmacodynamics blood samples should be drawn according to the schedule provided in Appendix B-3.

[v] Whole blood samples for assessment of anti-DCDS4501A or anti-obinutuzumab antibodies in serum will be drawn according to the schedule provided in Appendix B-3.

Appendix A-4
Study Flowchart: Post-Treatment Follow-Up for Rituximab-Containing Regimens (Arms A-B, Cohorts C-D)

Assessments/Procedures	Post-treatment Follow-up				
Months after treatment completion visit	2 Months	4 Months	6 Months	9 Months	12 Months
Targeted physical examination [a]	x	x	x	x	x
Vital signs (blood pressure, pulse rate, and body temperature)	x	x	x	x	x
ECOG Performance Status	x	x	x	x	x
B symptoms [b]	x	x	x	x	x
Tumor assessments [c]	x	x	x	x	x
Total IgA, IgG, IgM	x	x	x	x	x
Hematology [d]	x	x	x	x	x
Serum chemistry [e]	x	x	x	x	x
Bone marrow [f]	Perform to confirm CR if positive for disease at screening or if clinically indicated				
Central Lab Assessments					
Leukocyte immunophenotyping (FACS) [g]	x	x	x	x	x
Pharmacokinetic sampling [h]	x	x	x		
Serum sample for anti-DCDT2980S / anti-DCDS4501A ATA assay [h]	x	x	x		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATA = anti-therapeutic antibody; CR = completed response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; Ig = immunoglobulin; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography.

NOTE: Post-treatment assessments apply to patients who discontinue from study treatment (initial or crossover

treatment) for reasons other than disease progression. The schedule corresponds to visits timed from treatment completion/early termination visit or crossover treatment completion/early termination visit until the time of disease progression, start of new anti-cancer therapy, or withdrawal from study participation. Two-month and 4-month follow-up visits should occur within ±7 days from the scheduled date, while subsequent visits should occur within ±14 days from the scheduled date.

[a] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms.

[b] Defined as unexplained weight loss >10% over previous 6 months, fever (>38°C/100.4°F), and/or drenching night sweats.

[c] Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C).

[d] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[e] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), and uric acid.

[f] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[g] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[h] Refer to Appendices B-1 or B-2.

Appendix A-5
Study Flowchart: Post-Treatment Follow-Up for Obinutuzumab-Containing Regimens (Cohorts E, G-H)

Assessments/Procedures	Post-Treatment Follow-Up					
Months after treatment completion visit	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Targeted physical examination [a]	x	x	x	x	x	x
Vital signs (blood pressure, pulse rate, and body temperature)	x	x	x	x	x	x
ECOG Performance Status	x	x	x	x	x	x
Tumor Assessment (Imaging [PET/CT or C]) [b]		x		x	x	x
Total IgA, IgG, IgM	x	x	x	x	x	x
Hematology [c]	x	x	x	x	x	x
Serum chemistry [d]	x	x	x	x	x	x
Bone marrow [e]	Perform to confirm CR if positive for disease at screening or if clinically indicated					
Central Lab Assessments						
Leukocyte immunophenotyping (FACS) [f]	x	x	x	x	x	x
Pharmacokinetic sampling [g]	x	x		*x*	*x*	*x*
Serum sample for anti-DCDT2980S/anti-DCDS4501A, anti-obinutuzumab ATA assay [g]	x	x		x [g]	*x* [g]	x [g]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATA = anti-therapeutic antibody; CR = completed response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; Ig = immunoglobulin; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography.

NOTE: Post-treatment assessments apply to patients who discontinue from study treatment (initial or crossover treatment)

for reasons other than disease progression. The schedule corresponds to visits timed from treatment completion/early termination visit or crossover treatment completion/early termination visit until the time of disease progression, start of new anti-cancer therapy, or withdrawal from study participation. Two-month and four-month follow-up visits should occur within ±7 days from the scheduled date, while subsequent visits should occur within ±14 days from the scheduled date.

[a] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms.

[b] *Response should be assessed* using *Lugano Response C*riteria (Appendix C-2). CT or combined PET/CT scan should be obtained during the post-treatment follow-up *up every 6 months for 2 years or until study end or at any time that progression is suspected*.

[c] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[d] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid.

[e] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[f] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[g] Refer to Appendix B-3.

Appendix B-1
Serum and Plasma Pharmacokinetic Schedule for DCDT2980S/DCDS4501A and Rituximab, and ATA Schedule for DCDT2980S/DCDS4501A (For Patients Receiving Rituximab on Day 1 and DCDT2980S/DCDS4501A on Day 2 of Every Cycle) (Arms A-B, Cohorts C-D)

Study Visit	Sample Timepoint(s) [a]	Samples [b]
Cycle 1, Day 1	Pre-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycle 1, Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • DCDT2980S/DCDS4501A PK [b]
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 1, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 1, Day 15 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycles 2–3, Day 1	Pre-rituximab dose	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycles 2–3, Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 3, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 3, Day 15 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycles 4, and every 4th cycle thereafter), Day 1	Pre-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycles 4, and every 4th cycle thereafter), Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (± 15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK

Appendix B-1 (cont.)
Serum and Plasma Pharmacokinetic Schedule for DCDT2980S/DCDS4501A and Rituximab, and ATA Schedule for DCDT2980S/DCDS4501A (For Patients Receiving Rituximab on Day 1 and DCDT2980S/DCDS4501A on Day 2 of Every Cycle)

(Arms A-B, Cohorts C-D)

Study Visit	Sample Timepoint(s) [a]	Samples [b]
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK [e]
Post-treatment Follow-Up Visits [d]	2, 4, and 6 months after treatment completion visit	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Note: "Pre-infusion" means prior to the start of infusion; "Post-infusion" means after the infusion is completed.

[a] A 3-mL whole-blood sample will be taken for each of the following at each specified timepoint: anti-DCDT2980S or anti-DCDS4501A antibody; rituximab PK; and/or DCDT2980S/DCDS4501A PK. If rituximab dosing is split over two days, then PK will be obtained prior to the rituximab dose on the first day and 30 minutes (±15 minutes) post-rituximab infusion on the second day.

[b] PK sampling will not be obtained from patients who cross-over to another treatment arm.

[c] Cycles 2 and 4 only for anti-DCDT2980S or anti-DCDS4501A antibody.

[d] Post-treatment follow-up PK and ATA assessments only apply to patients who did not receive crossover treatment.

[e] DCDT2980S/DCDS4501A PK including serum PK samples for total DCDT2980S and DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

Appendix B-2
Serum and Plasma Pharmacokinetic Schedule for Rituximab and DCDT2980S/DCDS4501A, and ATA Schedule for DCDT2980S/DCDS4501A for Patients Receiving Rituximab and DCDT29808S/DCDS4501A on Day 1 of Every Cycle Beginning Cycle 3 (Arms A-B, Cohorts C-D)

Study Visit	Sample Timepoint(s) [a]	Samples [b]
For Cycle 1 and Cycle 2 PK assessments, refer to Appendix B-1		
Cycle 3, Day 1	Pre-rituximab infusion	• Rituximab PK • DCDT2980S/DCDS4501A PK [e]
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 3, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 3, Day 15 (±1 day)		• Rituximab • DCDT2980S/DCDS4501A PK
Cycles 4, and every 4th cycle thereafter), Day 1	Pre-rituximab infusion	• Rituximab PK • Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK
Post-treatment Follow-Up Visits [d]	2, 4, and 6 months after treatment completion visit	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK

Appendix B-2 (cont.)
Serum and Plasma Pharmacokinetic Schedule for Rituximab and DCDT2980S/DCDS4501A, and ATA Schedule for DCDT2980S/DCDS4501A for Patients Receiving Rituximab and DCDT29808S/DCDS4501A on Day 1 of Every Cycle Beginning **Cycle 3** (Arms A-B, Cohorts C-D)

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Note: "Pre-infusion" means prior to the start of infusion; "Post-infusion" means after the infusion is completed.

[a] A 3-mL whole-blood sample will be taken for each of the following at each specified timepoint: anti-DCDT2980S or anti-DCDS4501A antibody, rituximab PK, and/or DCDT2980S/DCDS4501A PK. If rituximab dosing is split over two days, then PK will be obtained prior to the rituximab dose on the first day and 30 minutes (±15 minutes) post-rituximab infusion on the second day.

[b] PK sampling will not be obtained from patients who cross-over to another treatment arm.

[c] Cycles 4 only for anti-DCDT2980S or anti-DCDS4501A antibody.

[d] Post-treatment follow-up PK and ATA assessments only apply to patients who did not receive crossover treatment.

[e] DCDT2980S/DCDS4501A PK including serum PK samples for total DCDT2980S and DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

Appendix B-3
Serum and Plasma Pharmacokinetic, Blood Pharmacodynamic, and ATA Schedule for Obinutuzumab and DCDS4501A (Cohorts E, G-H)

Study Visit	Sample Timepoint(s) [a]	Samples [a]
Cycle 1, Day 1	Pre-obinutuzumab infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • PD Blood [c]
	End of obinutuzumab infusion	• Obinutuzumab PK (serum) • PD Blood [c]
Cycle 1, Day 2	Pre-DCDS4501A infusion	• DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
	End of DCDS4501A infusion	• DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
Cycle 1, Day 8	6 days (±1 day) after Day 2 infusion	• DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
Cycle 1, Day 15	13 days (±1 day) after Day 2 infusion	• DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
Cycle 2, Day 1	Pre-obinutuzumab infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • PD Blood [c]
	End of obinutuzumab infusion	• PD Blood[c]
	Pre-DCDS4501A infusion	• DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
	End of DCDS4501A infusion	• PD Blood
Cycle 4, Day 1	Pre-obinutuzumab infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum)
	End of obinutuzumab infusion	• Obinutuzumab PK (serum)
	Pre-DCDS4501A infusion	• DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b]
	End of DCDS4501A infusion	• DCDS4501A PK (serum and plasma)[b]
Cycle 4 Day 15	Aligned with PET imaging	• PD Blood [c]
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b]
End of Treatment Assessment Visit	6–8 weeks after last study dose	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • PD Blood [c]

Appendix B-3 (cont.)

Serum and Plasma Pharmacokinetic and ATA Schedule for Obinutuzumab and DCDS4501A (Cohorts E, G-H)

Post-treatment Follow-Up Visits	3 and 6 months after treatment completion visit	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • PD Blood [c]
	9 months after treatment completion visit	• PD Blood [c]
	12 and 18 months after treatment completion visit	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • PD Blood [c]
	24 months after treatment completion visit	• *Obinutuzumab ATA (serum)* • *Obinutuzumab PK (serum)* • PD Blood [c]

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Note: "Pre-infusion" means prior to the start of infusion; "End-of-infusion" samples should be drawn 30 minutes (±15 minutes) unless otherwise specified.

[a] Up to 10-mL whole-blood samples will be taken for obinutuzumab PK, obinutuzumab ATA, obinutuzumab concentration, DCDS4501A PK (DCDS4501A total antibody, unconjugated MMAE and conjugate [evaluated as antibody-conjugated MMAE]), DCDS4501A ATA, DCDS4501A concentration, and for exploratory studies at each specified point with separate tubes for plasma or serum samples. If obinutuzumab dosing is split over two days, then PK will be obtained prior to the obinutuzumab dose on the first day and 30 minutes (±15 minutes) post-obinutuzumab infusion on the second day.

[b] DCDS4501A PK including serum PK samples for total DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

[c] Up to 10-mL whole-blood samples will be taken for exploratory studies at each specified timepoint with separate tubes.

Appendix C-1
Modified Response and Progression Criteria for NHL

Adapted from: Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol 2007;25:579–86.

Selection of Indicator (Target) Lesions

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions

  Abnormal lymph nodes are those that are either

  > 15 mm in the greatest transverse diameter (GTD) regardless of the short axis diameter, or

  > 10 mm in short axis diameter regardless of long axis

- If possible, they should be from disparate regions of the body.
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

PET Scans--Definition of a Positive PET scan

Visual assessment currently is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary. In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff. Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen uptake, and diffusely increased bone marrow uptake within weeks after treatment.

Complete Remission (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy.

   Typically FDG-avid lymphoma: in patients with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

   Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, the designation

of CR requires all nodal indicator lesions to regress to the size of normal lymph nodes. Lymph nodes that were >15 mm in GTD regardless of the short axis diameter at the screening tumor assessment must regress to ≤15 mm in GTD regardless of the short axis diameter. Lymph nodes that were 11 to 15 mm in GTD and >10 mm in the short axis diameter at the screening tumor assessment must regress to ≤10 mm in the short axis diameter.

2. The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

3. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (>20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial Remission (PR)

1. ≥50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; (b) if possible they should be from disparate regions of the body; (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

6. No new sites of disease should be observed (e.g., nodes >1.5 cm in any axis).

7. *Typically FDG-avid lymphoma*: for patients with no pretreatment PET scan or if the

PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. *Variably FDG-avid lymphomas/FDG-avidity unknown*: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

2. In patients with follicular lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease (SD)

1. Failing to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease (see below).

2. *Typically FDG-avid lymphomas*: the PET should be positive at prior sites of disease with no new areas of involvement on the post- treatment CT or PET.

3. *Variably FDG-avid lymphomas/FDG-avidity unknown*: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (RD; after CR) or Progressive Disease (PD; for Patients with PR or SD)

1. Lymph nodes should be considered abnormal if the long axis is $>$ 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1–1.5 cm, it should only be considered abnormal if its short axis is $>$ 1.0. Lymph nodes $\leq$ 1.0 cm by $\leq$ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

2. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities.

3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq$ 50% and to a size of 1.5 $\times$ 1.5 cm or more than 1.5 cm in the long axis.

4. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

5. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 15 mm in its long axis by CT).

6. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease.

Appendix C-2
Revised Criteria for Response Assessment: The Lugano Classification (Cohort E, G-H)

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol. 2014 Aug [cited 2014 Aug 29]. Available from: http://jco.ascopubs.org/content/early/2014/08/11/JCO.2013.54.8800.long.

Selection of measured dominant (indicator) lesions:

- Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters

  A measurable node must have an LDi greater than 1.5 cm.

  A measurable extranodal lesion should have an LDi greater than 1.0 cm.
- Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.
- Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation.
- If possible, they should be from disparate regions of the body.
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

Selection of non-measured (non-indicator) lesions:

- Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured.

  These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

Appendix C-2 (cont.)

Revised Criteria for Response Assessment: The Lugano Classification (Cohort E, G-H)

In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, and bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

Response	Site	PET-CT–based Response	CT-based Response
Complete		**Complete metabolic response**	**Complete radiologic response (all of the following)**
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS** It is recognizes that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to $\leq$ 1.5 cm in LDi No extralymphatic sites of disease
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial		**Partial metabolic response**	**Partial remission (all of the following)**
	Lymph nodes and extralymphatic sites	Score of 4 or 5** with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	$\geq$ 50% decrease in SPD of up to 6 target measureable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm $\times$ 5 mm as the default value When no longer visible, 0 $\times$ 0 mm For a node $>$ 5 mm $\times$ 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by $>$ 50% in length beyond

Appendix C-2 (cont.)

Revised Criteria for Response Assessment: The Lugano Classification (Cohort E, G-H)

Response	Site	PET-CT–based Response	CT-based Response
			normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease		**No metabolic response**	**Stable disease**
	Target nodes/nodal masses, extranodal lesions	Score 4 or 5** with no significant change in FDG uptake from baseline at interim or end of treatment	$<$50% decrease from baseline in SPD for up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Nonmeasured lesions	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease		**Progressive metabolic disease**	**Progressive disease (requires at least 1 of the following)**
	Individual target nodes/nodal lesions	Score 4 or 5** with an increase in intensity of uptake from baseline and/or	PPD progression: An individual node/lesion must be abnormal with: • LDi $>$1.5 cm AND • Increase by $\geq$50% from PPD nadir AND An increase in LDi or SDi from nadir • 0.5 cm for lesions $\leq$2 cm • 1.0 cm for lesions $>$2 cms
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	
	Nonmeasured lesions	None	New or clear progression of preexisting

Appendix C-2 **(cont.)**

Revised Criteria for Response Assessment: The Lugano Classification (Cohort E, G-H)

Response	Site	PET-CT–based Response	CT-based Response
	Organ enlargement		In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-acid foci	New or recurrent involvement

5-PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

**PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake < mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Appendix D
Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Appropriate monitors (electrocardiogram, blood pressure, pulse oximetry
- Oxygen
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines.
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional assistance!
- Maintain an adequate airway.
- Provide oxygen as needed.
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible.
- Administer antihistamines, epinephrine, inhaled bronchodilators, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix E
M. D. Anderson Symptom Inventory (MDASI)

M.D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24*** hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (symptom is as bad as you can imagine it could be) for each item.

	Not Present										**As Bad As You Can Imagine**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problems **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problems with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your **mouth/throat sores** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **diarrhea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your problems with **weakness in the arms or legs** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Appendix E (cont.)
M. D. Anderson Symptom Inventory (MDASI)

Part II. How have your symptoms interfered with your life?
Symptoms frequently interfere with how you feel and function. How much have your symptoms interfered with the following items **in the last 24** hours:

	Did Not Interfere										Interfered Completely
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
18. General activity?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
19. Mood?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
20. Work (including work around the house)?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
21. Relations with other people?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
22. Walking?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
23. Enjoyment of life?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Appendix F
Recommendations for the Use of White Blood Cell Growth Factors

Primary Prophylactic G-CSF Administration (First and Subsequent-Cycle Use)

Primary prophylaxis with G-CSF is recommended if any of the following clinical factors are present:

- Age >65 years
- Poor performance status
- Previous history of febrile neutropenia
- Open wounds or active infections
- More advanced cancer
- Extensive prior treatment, including large radiation therapy ports
- Cytopenias due to bone marrow involvement by tumor
- Other serious comorbidities

Secondary Prophylactic G-CSF Administration

Prophylactic G-CSF administration is recommended for patients who fulfill each of the following circumstances:

- Experienced a neutropenic complication from a prior cycle of study treatment
- Primary prophylactic G-CSF was not received; and
- The intent is to avoid dose reduction of the antibody–drug conjugate (ADC), where the effect of the reduced dose on disease-free, overall survival or treatment outcome is not known

Therapeutic Use of G-CSF

G-CSF administration should be considered for the following patients:

- Patients with febrile neutropenia who are at high risk for infection-associated complications; or
- Patients who have prognostic factors that are predictive of poor clinical outcome, e.g., prolonged (>10 days) and profound (<100/μL) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of fever development

Source: Smith TJ et al. 2006 Update of Recommendations for the use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. JCO 24:3187-3205. 2006.

PROTOCOL

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF *PINATUZUMAB VEDOTIN* (DCDT2980S) IN COMBINATION WITH RITUXIMAB OR *POLATUZUMAB VEDOTIN* (DCDS4501A) IN COMBINATION WITH RITUXIMAB *AND A NON-RANDOMIZED PHASE Ib/II EVALUATION OF POLATUZUMAB VEDOTIN IN COMBINATION WITH OBINUTUZUMAB* IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
EUDRACT NUMBER:	2011-004377-84
STUDY DRUG:	*Pinatuzumab Vedotin (*DCDT2980S*)*; *Polatuzumab Vedotin (*DCDS4501A*)*
IND:	107713
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	27 July 2012
DATE AMENDED:	Version A1: 24 June 2013 Version A2: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Clinical Science Leader	06-Nov-2014 16:11:09

PROTOCOL AMENDMENT, VERSION A2:
RATIONALE

Protocol GO27834 has been amended to enable the following changes:

- Obinutuzumab, a novel type II and glycoengineered anti-CD20 antibody, is currently being compared with rituximab in two large Phase III studies in patients with diffuse large B-cell lymphoma (DLBCL) and indolent non-Hodgkin's lymphoma (iNHL), potentially altering the standard of care in NHL. A Phase Ib/II portion of the study will be added using obinutuzumab in combination with polatuzumab vedotin (DCDS4501A). Initially, a safety run-in of 6 patients with either relapsed or refractory follicular NHL or DLBCL will be treated with DCDS4501A at 1.8 mg/kg in combination with obinutuzumab (denoted as Cohort E). Only patients in the United States will participate in this portion of the study. If this cohort safely clears, the expansion portion of the study will further evaluate the safety, tolerability, and clinical activity of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in patients with relapsed or refractory follicular NHL or DLBCL. The expansion cohorts will contain 40 patients for each histology, follicular NHL or DLBCL (denoted Cohorts G and H). Only investigator sites in the United States and Canada will participate in this portion of the study.
- For obinutuzumab-containing cohorts (Cohorts E*,* G, and H), PET/CT scans will be required for both follicular NHL and DLBCL at screening, interim response assessment (between Cycle 4 Day 15 and Cycle 5 Day 1), and end of treatment (EOT) assessment. In the post-treatment follow-up period, patients will be followed for response for up to 2 years after the last infusion of study treatment.
- The response criteria for NHL have been updated in Appendix C-2.
- DCDT2980S is also known as pinatuzumab vedotin and will be referred to as DCDT2980S throughout this protocol.
- DCDS4501A is also known as polatuzumab vedotin and will be referred to as DCDS4501A throughout this protocol.
- Arms A and B are no longer open and no longer enrolling patients.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION A2:
SUMMARY OF CHANGES

GLOBAL CHANGES

The title of the protocol has been changed.

DCDT2980S is also known as pinatuzumab vedotin and will be referred to as DCDT2980S throughout this protocol.

DCDS4501A is also known as polatuzumab vedotin and will be referred to as DCDS4501A throughout this protocol.

The Medical Monitor has been changed to [redacted], M.D.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2.4: *Obinutuzumab*

SECTION 1.2.4.1 *Obinutuzumab Mechanism of Action*

Obinutuzumab ([G], also known as RO5072759, GA101, Gazyva™, and Gazyvaro™) is a humanized type II and glycoengineered anti-CD20 MAb, derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics (Mössner et al. 2010; Golay et al. 2013):

- *High-affinity binding to CD20 antigen on B cells*
- *Type II binding mode to the CD20 antigen, leading to a more even distribution of bound antibody to the surface membrane of the B cell due to lack of CD20 translocation into lipid rafts after antibody binding and low complement activation and low complement-dependent cytotoxicity related to the recognition of the CD20 epitope*
- *Compared with the type I anti-CD20 antibodies rituximab or ofatumumab, increased ADCC and antibody-dependent cell-mediated phagocytosis (ADCP) related to an improved binding of obinutuzumab to the different allotypes of FcγRIIIa and FcγRIIIb expressed by natural killer (NK) cells , monocytes/macrophages and neutrophils*
- *Compared with rituximab, increased direct cell-death induction related to an elbow hinge amino exchange of the Fab region and type II binding of the CD20 epitope*

Obinutuzumab received FDA approval in November 2013 and EMA approval in July 2014 on the basis of the CLL-11 Study BO21004 for patients with relapsed Chronic Lymphocytic Leukemia. Obinutuzumab plus chlorambucil showed superiority over rituximab plus chlorambucil in all efficacy parameters such as overall response rate (ORR), complete remission rate (CRR), minimal residual disease (MRD),

progression-free survival (PFS), event-free survival (EFS), and duration of response (DOR) (Goede et al. 2014).

Obinutuzumab is currently being explored in the treatment of lymphoid malignancies such as aggressive and indolent lymphomas (DLBCL, FL, and marginal zone lymphoma [MZL]). Preliminary data suggest possible increased anti-lymphoma efficacy over rituximab, a hypothesis that is currently being explored in several randomized trials, including a Phase III study of R-CHOP versus G-CHOP in first-line treatment of DLBCL, a Phase III study of R-chemotherapy (CHOP, CVP, or bendamustine) followed by rituximab maintenance compared with G-chemotherapy (CHOP, CVP, or bendamustine) followed by obinutuzumab maintenance in first-line treatment of FL and MZL, and a Phase III study of obinutuzumab combined with bendamustine compared with bendamustine in patients with rituximab-refractory indolent NHL.

SECTION 1.2.4.2 *Obinutuzumab Nonclinical Toxicology*

The nonclinical toxicology of obinutuzumab has been evaluated in repeat-dose studies in cynomolgus monkeys given weekly IV (30-minute infusion) up to 26 weeks in duration and weekly SC injections for 4 weeks in duration. The high dose of 50 mg/kg in the 26-week study resulted in a steady-state area under the concentration-time curve from 0 to 24 hours (AUC_{0-24}) exposure of 341,000 $\mu g \cdot hr/mL$, which is approximately 61-fold above that of the clinical exposure of 5584 $\mu g \cdot hr/mL$.

Consistent with expected pharmacologic activity, obinutuzumab caused marked decreases in B cells, with corresponding lymphoid depletion in spleen and lymph nodes. Circulating CD40-positive mature B cells began to reverse after several months without treatment and maximally reversed to 7%–152% of baseline by 37 weeks. In addition, transient decreases in NK cells were observed; this finding is consistent with the pharmacologic effect of FcγRIIIa binding. Suspected opportunistic infections in as many as three unscheduled deaths were considered a possible secondary result of B-cell depletion.

Obinutuzumab was immunogenic in the cynomolgus monkey, which led to reduced systemic exposures in several animals and abrogation of the pharmacologic activity. Hypersensitivity reactions were noted that included systemic inflammation and infiltrates consistent with immune complex–mediated hypersensitivity reactions such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation and led to unscheduled termination in six animals.

Both the clinical IV formulation and the SC formulation of obinutuzumab were locally well tolerated across studies. No effects were present in male and female reproductive parameters included in the 26-week IV dose study. No obinutuzumab-related effects were observed on CNS, respiratory, or cardiovascular function.

In vitro assays using undiluted human whole blood measured significant increases in cytokine secretion caused by obinutuzumab, indicating that obinutuzumab has an increased propensity to trigger first infusion–related cytokine release in patients.

See the Obinutuzumab Investigator's Brochure for details on the nonclinical studies.

SECTION 1.2.4.3 *Obinutuzumab Nonclinical Efficacy*

Obinutuzumab has in vivo efficacy superior to rituximab in various human lymphoma xenograft models. Both antibodies were tested in human SUDHL-4 cells (DLBCL model) injected subcutaneously in severe combined immunodeficient (SCID) beige mice. Rituximab administration was started when tumors were established and rapidly growing. Results showed that rituximab at 10 mg/kg inhibited tumor growth compared with rituximab at 1 mg/kg; however, increasing the rituximab dose to 30 mg/kg did not result in increased efficacy and rituximab was not able to achieve complete tumor regression. In contrast, obinutuzumab showed a dose-dependent increase in efficacy in the range of 1–30 mg/kg. Results showed complete tumor regression in all animals and lasting tumor eradication in 9 of 10 animals at the highest dose of 30 mg/kg and in 1 of 10 animals at a dose of 10 mg/kg.

In another experiment, SUDHL4 xenografts in SCID mice were first treated with weekly rituximab 30 mg/kg. When the tumors became refractory to rituximab (Day 35), rituximab treatment was continued or changed to either weekly vehicle control or obinutuzumab 30 mg/kg. While tumors in control- and rituximab-treated mice continued to grow, obinutuzumab-treated mice showed control of tumor growth and lived until Day 61 when control or rituximab-treated mice had already been sacrificed.

Additional studies have also shown similar results, with obinutuzumab treatment controlling tumor growth, whereas vehicle- and rituximab-treated tumors were not controlled (Mössner et al. 2010).

See the Obinutuzumab Investigator's Brochure for details on the nonclinical studies.

SECTION 1.2.4.4 *Obinutuzumab Clinical Experience*

As of July 2013, more than 1900 patients with CD20-positive malignant disease have been treated with obinutuzumab in clinical trials. Clinical data for obinutuzumab are available from six clinical trials, including three Phase I and Phase II studies of obinutuzumab monotherapy, a Phase Ib chemotherapy combination study in NHL (Study BO21000), and two Phase III studies (Study BO21004 in CLL and Study GAO4753g in NHL).

Infusion-related reactions (IRRs), mostly Grades 1 and 2, are the most common adverse events observed during therapy. IRRs have been associated predominantly with the first infusion, generally occurring early during the infusion, shortly after the infusion,

or, in some cases, up to 24 hours after the completion of the infusion. In a few patients, concurrent signs of laboratory tumor lysis syndrome (TLS) were observed. The incidence and intensity of IRRs decreased strongly with subsequent infusions of obinutuzumab. On the basis of preliminary observations, extensive tumor burden, tumor factors, and host factors may be predisposing factors for the occurrence of IRRs. The frequency and severity of IRRs is also reduced in lymphomas compared with CLL.

Other frequently observed adverse events include infections and neutropenia. Grade 3–4 thrombocytopenia and neutropenia, including febrile neutropenia, have been reported with obinutuzumab, associated predominantly with treatment of CLL rather than NHL. Given its anticipated mode of action, which results in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections during and after treatment.

Data from Study BO20999 (obinutuzumab monotherapy) showed safety and efficacy of single-agent obinutuzumab in patients with relapsed indolent and aggressive lymphomas. Responses were seen at both lower (400 mg) and higher (1600/800 mg) doses, although responses increased at the higher dose, with 54% of patients with indolent lymphoma and 32% of patients with aggressive lymphomas showing PR or CR at the end of treatment (EOT) (Morschhauser et al. 2013; Salles et al. 2013).

Study BO21000 (Phase Ib) evaluated obinutuzumab in combination with chemotherapy: obinutuzumab with fludarabine and cyclophosphamide and obinutuzumab with CHOP (Radford et al. 2013). Both chemotherapy combinations were shown to be feasible in patients with previously untreated or relapsed or refractory FL, with response rates of >90% for both regimens. Safety was acceptable, with no new or unexpected adverse events observed. The most common adverse event was neutropenia.

Data from obinutuzumab in combination with chlorambucil in CLL (Phase III Study BO21004) showed increased efficacy of this combination over rituximab-chlorambucil, with a hazard ratio of 0.39 for PFS. IRRs were common (65% all grades, 20% Grade 3–4, no fatal IRRs) and neutropenia occurred at increased frequency with the combination therapy (33% Grade 3–5), but there was no increase in infections or treatment-related deaths (Goede et al. 2014).

See the Obinutuzumab Investigator's Brochure for additional details on the clinical studies.

SECTION 1.2.4.5 *Obinutuzumab Pharmacokinetics and Pharmacodynamics*

A two-compartment model comprising a time-varying CL pathway and a linear CL pathway provides an adequate description of the pharmacokinetics of obinutuzumab following IV administration in Study BO20999 and Study BO21003. Following the infusion of obinutuzumab, the elimination appears to be characterized by a linear CL pathway that is dependent on time (i.e., starting at a typical value of 630 mL/day and

then gradually decreasing to an asymptote of 60 mL/day at steady state). Tumor burden may potentially contribute significantly to the CL of obinutuzumab, especially at the beginning of treatment when CD20-positive tumor cells are most abundant. As tumor burden decreases, the CL reaches an asymptote, which is considered to be primarily a function of the proteolytic metabolic CL. Some patients with a high tumor burden may appear to clear the drug from the plasma faster than patients with a low tumor burden because obinutuzumab binds to the CD20-positive tumor cells and is effectively removed from the plasma. The CL of the drug will vary with time because repeated treatments with obinutuzumab will reduce the quantity of CD20-positive tumor cells. The number of times obinutuzumab is administered during the first cycle of treatment may be expected to reduce the number of CD20-positive tumor cells, thus minimizing the impact of the time-varying CL pathway on obinutuzumab exposure.

Treatment with obinutuzumab resulted in extensive B-cell depletion, with all patients showing a reduction in B-cell counts to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before and after infusion, but transient increases occurring during the administration of obinutuzumab have been observed in the levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-10, and interferon (IFN)-γ.

SECTION 1.3: RATIONALE FOR DOING THIS STUDY

The goals of this ~~Phase II~~ study are to continue to assess the safety, tolerability, and biologic and clinical activity of the combinations of DCDT2980S and rituximab and DCDS4501A and rituximab in two specific NHL patient populations: patients with relapsed or refractory follicular NHL and patients with relapsed or refractory DLBCL. *An additional goal of this study is to assess the safety, tolerability, and potential biologic and clinical activity of DCDS4501A in combination with obinutuzumab, an anti-CD20 antibody, in the aforementioned NHL patient populations.* These patients continue to have an extremely poor prognosis with no curative options available. Consequently, new therapeutic options are needed.

DCDT2980S, DCDS4501A ~~and~~*,* rituximab, *and obinutuzumab* each target antigens specific to B-cell malignancies including follicular NHL and DLBCL (see Figures 1 and 2).

The randomized component of the Phase II study design permits an assessment of the clinical benefit provided by each of these molecules in combination with rituximab, which has established clinical activity in B-cell malignancies both as monotherapy and in combination with chemotherapy. Data from this study will help inform the feasibility of the combination regimens in earlier lines of therapy (e.g., as first-line therapy in newly diagnosed patients).

The non-randomized component of the study will further evaluate the safety and tolerability and clinical activity of DCDS4501A in combination with obinutuzumab in

patients with relapsed or refractory follicular lymphoma or DLBCL and will also provide preliminary evidence as to which anti-CD20 agent, rituximab or obinutuzumab, in combination with DCDS4501A, provides a better benefit-risk profile in the target population being studied.

Given the relatively poor prognosis of patients with relapsed or refractory hematologic malignancies that have failed standard therapies, the nonclinical toxicity profile associated with DCDT2980S and DCDS4501A treatment, and the clinical safety profile observed to date for both ADCs, the benefit-risk ratio of a clinical study of DCDT2980S and DCDS4501A, each combined with rituximab *or obinutuzumab*, is considered acceptable.

SECTION 1.3.2: *Rationale for Assessing DCDS4501A in Combination with Obinutuzumab in Relapsed or Refractory NHL*

The development of next-generation anti-CD20–directed therapy may further enhance the efficacy of current standard regimens for NHL. Obinutuzumab, also known as RO5072759, GA101, and Gazyva™/Gazyvaro™, a novel type II and glycoengineered anti-CD20 antibody, has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). Obinutuzumab is currently being compared with rituximab in two large Phase III studies in patients with newly diagnosed DLBCL (Study BO21005) and with previously untreated iNHL, including FL (Study BO21223). Assuming these studies demonstrate greater clinical benefit with obinutuzumab- vs. rituximab-containing regimens, potentially altering the standard of care in NHL, it will be important to also assess the safety and efficacy of combining DCDS4501A with obinutuzumab-containing regimens.

The goals of the non-randomized portion of the Phase Ib/II study are to assess the safety, tolerability, and potential biologic and clinical activity of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in patients with relapsed or refractory follicular NHL or DLBCL. The RP2D, the Phase II dose-expansion portion of the study, will further evaluate the safety and tolerability and clinical activity of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in patients with relapsed or refractory follicular NHL or DLBCL.

SECTION 2.1: PRIMARY OBJECTIVES

The primary objectives of this study are the following:

- *To assess the safety and tolerability of the combination of DCDS4501A and obinutuzumab when administered to patients with relapsed or refractory follicular NHL or DLBCL*
- *To assess the anti-tumor activity of the combination of DCDS4501A and obinutuzumab in patients with relapsed or refractory follicular NHL and DLBCL*

SECTION 2.2.1: Safety Objectives

The secondary safety objectives of this study are the following:

- To assess the incidence of antibody formation to DCDT2980S, ~~and~~ DCDS4501A*, and obinutuzumab as measured by the formation of ATAs*
- To compare the safety and tolerability of the combination of DCT2980S and rituximab and DCDS4501A and rituximab *or obinutuzumab*

SECTION 2.2.2: Activity Objective

The secondary activity objective of the study is the following:

- To compare the anti-tumor activity of the combination of DCT2980S and rituximab and DCDS4501A and rituximab *or obinutuzumab*

SECTION 2.2.3: Pharmacokinetic Objectives

The PK objectives of this study are the following:

- To characterize the pharmacokinetics of DCDS4501A and rituximab *or obinutuzumab* in patients with relapsed or refractory NHL when the two drugs are given in combination

SECTION 2.3.1: Biomarker Objectives

The objectives of this study related to assessment of biologic markers are the following:

- To make a preliminary assessment of biologic markers that might act as predictors of DCDS4501A + rituximab *or obinutuzumab* combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL

SECTION 2.3.2: Patient-*Reported Outcomes Objective* ~~Quality of Life Objective~~

The objective of this study related to assessment of ~~patient quality of life~~ *patient-reported outcomes (PRO)* is the following:

- To assess patient-*reported* tolerability to study treatment and the impact of study treatment on patient ~~quality of life~~*functioning* on the basis of ~~patient reported outcomes (~~PRO~~)~~

SECTION 3.1: DESCRIPTION OF THE STUDY

This is a Phase *Ib/*II, multicenter, open-label study. *Up to approximately 252* ~~A total of approximately 140–160 patients (approximately 60–80 patients with relapsed or refractory follicular NHL and approximately 80~~ patients with relapsed or refractory *FL and* DLBCL~~)~~ will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data. *Arms A and B and Cohort C are no longer enrolling patients.*

For Obinutuzumab Cohorts:

Only investigational sites in the United States will enroll patients into Cohort E. Investigational sites in the United States and Canada will participate in Cohorts G and H).

SECTION 3.1.1: ***Rituximab-Containing Regimens with DCDT2980S or DCDS4501A***

SECTION 3.1.1.2: Non-Randomized Portion of the Study *with Rituximab* **(Cohorts C and D)**

SECTION 3.1.2: <u>All Patients</u> ***<u>on Rituximab-Containing Arms/Cohorts</u>***

All patients *on rituximab-containing regimens*, regardless of assigned arm/cohort, will receive DCDT2980S or DCDS4501A and rituximab administered by IV infusion on a 21-day cycle.

Patients will be evaluated for safety and efficacy according to the Schedules of Assessments outlined in Appendices A-1, A-2, and ~~A-3~~ *4*. Initial response assessments in this study will be performed every 3 months from the initiation of therapy until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). Additional response assessments for patients who proceed to crossover treatment (see Section 3.1.6) will be performed as described in Appendix A-2; response assessments for patients who discontinue study treatment (both initially assigned treatment and crossover treatment) for reasons other than disease progression will be performed as described in Appendix ~~A-3~~ *4*.

SECTION 3.1.3: ***<u>Obinutuzumab-Containing Regimen with DCDS4501A (Cohorts E, G, and H)</u>***

DCDS4501A at 1.8 mg/kg will be given in combination with obinutuzumab to patients with relapsed or refractory follicular NHL and DLBCL in two stages: (1) safety run-in and (2) expansion.

Study treatment will be given in 21-day cycles for both follicular NHL and DLBCL. Patients will be treated for up to a total of 8 cycles. For the first cycle, obinutuzumab will be administered by IV infusion on Days 1, 8, and 15. DCDS4501A will be given on Day 2 for Cycle 1. In the absence of any infusion-related adverse events, obinutuzumab and DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the second cycle. If obinutuzumab and DCDS4501A are administered on the same day, the study drugs will be given sequentially. Obinutuzumab will be administered first, followed by DCDS4501A. In certain circumstances—for example, IRRs requiring interruption or slowing of infusion rate—obinutuzumab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDS4501A may be administered on Day 2 following completion of the obinutuzumab infusion.

SECTION 3.1.3.1: ***Obinutuzumab-Containing Regimens in Phase Ib: Safety Run-in (Cohort E)***

This portion of the study will consist of a safety run-in that will evaluate the safety of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in 6 patients (Cohort E). The safety run-in is described in detail in Section 3.4. In case an amendment to the protocol allows to study higher doses of DCDS4501A, the safety run-in for the 1.8 mg/kg may be shortened to 3 patients.

Obinutuzumab-Containing Regimens in Phase II: Expansion Stage (Cohorts G and H)

After the safety run-in has demonstrated that DCDS4501A at 1.8 mg/kg in combination with obinutuzumab is safe to administer, patients will be enrolled into two expansion cohorts based on histology of follicular NHL or DLBCL (Cohorts G and H, respectively). Forty patients will be enrolled into each expansion cohort. An additional cohort(s) may be added in the future.

SECTION 3.1.4: **Follicular NHL ~~Cohort~~** ***Patients for Rituximab-Containing Arms/Cohorts***

SECTION 3.1.5: ***Follicular NHL Patients for Obinutuzumab-Containing Cohorts***

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- *Relapsed to prior regimen(s) after having a documented history of response (CR, CRu, or PR) of ≥6 months in duration from completion of regimen(s)*
- *Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy*

SECTION 3.1.6: **DLBCL ~~Cohort~~** ***Patients for Rituximab-Containing Arms/Cohorts***

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/stem cell transplant (SCT) ~~as determined by the investigator~~ will be enrolled into the study as defined by the following:

SECTION 3.1.7: ***DLBCL Patients for Obinutuzumab-Containing Cohorts***

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/SCT as determined by the investigator will be enrolled into the study as defined by the following:

- *Second-line SCT-ineligible patients with progressive disease or no response (SD) <12 months from start of initial therapy (second-line refractory)*
- *Second-line SCT-ineligible patients with disease relapse after initial response ≥12 months from start of initial therapy (second-line relapsed)*
- *Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) <6 months from start of prior therapy (third-line +refractory)*

- *Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response ≥6 months from start of prior therapy (third-line + relapsed)*

SECTION 3.1.8: Crossover Treatment (Randomized Patients *in Arms A and B* Only)

Patients will be treated with the crossover treatment until a second disease progression event relative to the tumor assessment, documenting progressive disease on the initial study treatment, clinical deterioration, and/or intolerance to the crossover treatment for up to a maximum of 1 year (17 cycles on an every-21-day schedule). Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in Appendices A-2. Response assessments for patients who discontinue study treatment for reasons other than disease progression will be performed as described in Appendix A-~~3~~*4*.

Clinical data and exploratory data derived from tumor biopsies obtained prior to crossover treatment will be monitored on an ongoing basis. Genentech has the right to restrict or suspend enrollment into crossover treatment at any time. Reasons for this may include, but are not limited to, the following:

- Patients who are enrolled into the non-randomized portion of the study (Cohorts C, D, *E, G, and H*) will not have the option to receive crossover treatment upon disease progression (see Section 3.2 for rationale).

SECTION 3.2: RATIONALE FOR STUDY DESIGN

The primary rationale for the non-randomized portion of the study *(Cohorts C and D)* is to assess the therapeutic index (i.e., the balance of efficacy and tolerability of DCDT2980S and DCDS4501A at a dose of 1.8 mg/kg in patients with relapsed or refractory follicular NHL). An informal comparison between patients with follicular NHL treated at the two doses of the ADC will help determine if tolerability is improved at the lower ADC dose without substantial compromise of efficacy.

The primary rationale for the non-randomized Phase Ib/II obinutuzumab-containing cohorts (Cohorts E–H) is to assess safety and clinical activity for the combination of obinutuzumab and DCDS4501A in patients with relapsed/refractory NHL (Cohorts E, G, and H). Obinutuzumab (also known as RO5072759, GA101 and Gazyva™/Gazyvaro™), a novel type II and glycoengineered anti-CD20 antibody, has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). Obinutuzumab is currently being compared with rituximab in two large Phase III studies in patients with newly diagnosed DLBCL (Study BO21005) and previously untreated iNHL, including FL (Study BO21223). Assuming these studies demonstrate greater clinical benefit with obinutuzumab- vs. rituximab-containing regimens, potentially altering the standard of care in NHL, it will be important to also assess the safety and efficacy of combining DCDS4501A with obinutuzumab-containing regimens.

Study drug dosing will occur on Days 1 *or* ~~and~~ 2 of each 21-day (or 28-day) cycle to allow for recovery from potential bone marrow toxicity.

SECTION 3.2.1: Rationale for the PK Sample Schedule

PK data obtained in this study will be important in informing potential future trials with this combination. Given the likely changing effect of peripheral B-cell counts, tumor burden, and target antigen expression on target-mediated drug CL over multiple doses of DCDT2980S or DCDS4501A plus rituximab *or obinutuzumab* when the two drugs are given in combination, the drug levels of DCDT2980S or DCDS4501A-related analytes and rituximab *or obinutuzumab* will be assessed in this combination study.

In Studies DCT4862g and DCS4968g, single-agent DCDT2980S and DCDS4501A administered by IV infusion every 21 days were evaluated at doses ranging from 0.1 to 3.2 mg/kg for DCDT2980S and 0.1 mg/kg to 2.4 mg/kg for DCDS4501A in patients with NHL. Intensive PK sampling of all patients in the ongoing Phase I studies will provide sufficient data to allow complete profiling of the distribution and elimination phases for DCDT2980S and DCDS4501A and the investigation of potential correlations between various PK parameters and efficacy and/or toxicity. Consequently a reduced PK sampling scheme of DCDT2980S and DCDS4501A will be used in this ~~Phase II~~ study.

The PK data collected in this ~~Phase II~~ study will allow further characterization of the PK properties of DCDT2980S and DCDS4501A. In addition, the DCDT2980S and DCDS4501A concentration results from this study will be compared with available data from the single-agent clinical studies to evaluate whether concurrent administration of rituximab affects the exposure of DCDT2980S and/or DCDS4501A.

Limited sampling of serum concentrations of obinutuzumab will be assessed and compared with historical data to evaluate potential PK interactions with DCDS4501A.

SECTION 3.3.1: Safety Outcome Measures

The safety and tolerability of the combination of DCDT2980S and rituximab and DCDS4501A and rituximab *or obinutuzumab* will be assessed using the following safety outcome measures:

- Incidence of anti-DCDT2980S ~~or~~*,* anti-DCDS4501A*, or anti-obinutuzumab* antibodies

SECTION 3.3.2: Pharmacokinetic/Pharmacodynamic Outcome Measures

The following PK parameters will be derived from the serum concentration-time profiles of total antibody (the sum of conjugated and unconjugated antibody), including rituximab *or obinutuzumab*, and plasma concentration-time profiles of acMMAE and free MMAE following administration of DCDT2980S or DCDS4501A, when appropriate, as data allow:

The following PD outcome measures will be assessed when appropriate, as data allow:

- *Assessment of the kinetics of circulating tumor DNA*

SECTION 3.3.3: Activity Outcome Measures

The following activity outcome measures will be assessed:

- Duration of objective response, defined as the *duration of time from the* first occurrence of a documented objective response *to*~~until the~~ time of relapse or death from any cause
- PFS, defined as the *duration from initial* ~~date of~~ randomization to the first occurrence of progression or death within 30 days of the last administration of study drug, whichever occurs first
- OS, defined as the *duration* ~~time~~ from the date of randomization*/enrollment* to the date of death from any cause

SECTION 3.3.4: Exploratory Outcome Measures

The exploratory outcome measures will include, but will not be limited to, the following:

- Additional assessments related to the understanding of the mechanism of action of DCDT2980S, DCDS4501A, ~~and~~ rituximab, *and obinutuzumab*, *e.g., assessment of circulating tumor DNA(ctDNA) to monitor response*, mechanisms of resistance to DCDT2980S, DCDS4501A ~~and~~*,* rituximab, *and obinutuzumab*, and/or NHL pathogenesis may be included.
- ~~Quality of life~~*Treatment and disease symptom* assessments using the M.D. Anderson Symptom Inventory (MDASI)

SECTION 3.4: SAFETY PLAN

Safety will be evaluated through the monitoring of the following:

- All adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A ~~or~~*,* rituximab, *or obinutuzumab,* whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A ~~or~~*,* rituximab, *or obinutuzumab,* whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from the last dose of DCDT2980S, DCDS4501A ~~or~~*,* rituximab, *or obinutuzumab,* whichever is later, including doses that were administered as part of crossover treatment, and which are judged to be caused by DCDT2980S, DCDS4501A ~~or~~*,* rituximab, *or obinutuzumab*, regardless of time of onset

SECTION 3.4.1: *Safety Run-In Analysis*

As outlined in Figure 3b and Section 3.1.3.1, a safety run-in analysis (Cohort E) will be conducted by the Internal Monitoring Committee (IMC) to evaluate the combination of DCDS4501A at a dose of 1.8 mg/kg with obinutuzumab. This analysis will include data from the first 6 patients treated through Day 21 of Cycle 1. Three patients will initially be enrolled, and then an additional 3 patients will be enrolled after the first 3 patients have safely completed the first cycle. At the IMC's discretion, and at any

point during enrollment of the safety run-in, a decision could be made that more than 6 patients are needed to evaluate safety. In this case, the protocol will be amended to allow for more than 6 patients in the safety run-in. In case the study is amended to test additional doses the safety run-in for 1.8 mg/kg may be shortened to three patients.

Safety summaries will be assessed at the safety run-in for SAEs; Grade 3-5 treatment-related AEs; all AEs; all Grade 3-5 AEs; and AEs leading to treatment discontinuation or dose modification/interruption.

- *During the 6-patient safety run-in, if any patient experiences a treatment-related death, then the obinutuzumab-containing portion of the study will be closed to further recruitment.*
- *During the 6-patient safety run-in:*

  If 2 or more of the first 3 patients enrolled experience Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment

  If 1 of the first 3 patients enrolled experiences Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then an additional 3 patients will be recruited. If 2 or more of these first 3 patients experience Grade 4 febrile neutropenia or serious (i.e., SAE) infection with Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment.

  If 2 or more of the first 6 patients to be enrolled experiences Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment.

  Before the expansion portion of the study can begin (enrollment of Cohorts G and H), the following criteria must be met:

    Six patients must have competed enrollment in the safety run-in (Cohort E).

    Three patients must have completed at least 4 cycles of treatment.

SECTION 3.4.2: Internal Monitoring Committee

In addition to the ongoing assessment of the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities by the Investigator and the Medical Monitor, the IMC will review the aforementioned data at least twice during the study.

Throughout the course of the study, the IMC will meet, as needed, at the request of the Medical Monitor (e.g., on the basis of unexpected safety signals). The IMC may make

recommendations regarding study conduct, including, but not limited to, performing additional safety analyses, amending the study protocol, holding patient enrollment to one or both treatment arms pending further safety evaluations, holding/discontinuing study treatment, or terminating the study.

Complete details of the IMC will be described in the IMC charter.

For Arms A and B: The first planned review will occur after approximately 10 patients are randomized and have at least 6 weeks follow-up, and the next formal review will occur when approximately 60 patients are randomized and have at least 6 weeks follow-up. ~~Additionally, the IMC will meet as needed at the request of the Medical Monitor (e.g., on the basis of unexpected safety signals). The IMC may make recommendations regarding study conduct, including, but not limited to, performing additional safety analyses, amending the study protocol, holding patient enrollment to one or both treatment arms pending further safety evaluations, holding/discontinuing study treatment, or terminating the study.~~

~~Complete details of the IMC will be described in the IMC charter.~~

SECTION 3.4.3.3: Bone Marrow Toxicity/Neutropenia

Adequate hematologic function should be confirmed before initiation of study treatment. Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. *Study treatment may be delayed or modified due to* ~~Treatment for~~ hematologic toxicities*,* ~~may be delayed or modified~~ as described in Section 4.3.1.

Febrile neutropenia is commonly associated with myelotoxicity, which is considered a class effect of MMAE because it is commonly reported with ADCETRIS®, other similar ADCs, and vincristine sulfate.

Clinical data show that among the most common SAEs reported in both DCS4968g and DCT4862g studies were febrile neutropenia and pyrexia.

SECTION 3.4.3.4: Immunogenicity

As expected with any recombinant antibody, DCDT2980S*,* ~~and~~ DCDS4501A*, and obinutuzumab* may elicit an immune response and patients may develop antibodies against DCDT2980S*,* ~~and~~ DCDS4501A*, or obinutuzumab*. Patients will be closely monitored for any potential immune response to DCDT2980S*,* ~~and~~ DCDS4501A*, and obinutuzumab*. Appropriate screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with DCDT2980S*,* ~~or~~ DCDS4501A*, and obinutuzumab*. Considering the historically low immunogenicity rate of rituximab in NHL patients, ATAs against rituximab will not be monitored in this study.

SECTION 3.4.3.5: Peripheral ~~Sensory~~ Neuropathy

On the basis of clinical data from the ongoing Phase I Studies DCT4862g and DCS4968g and data from brentuximab vedotin studies, an anti-CD30-vc-MMAE ADC (see Section 3.4.2), peripheral ~~sensory~~ neuropathy *(sensory and motor)* has been identified as a known risk (adverse drug reaction) for both DCDT2980S and DCDS4501A.

Careful clinical evaluation of patients for neuropathy should be conducted prior to initiation of study drug. Patients should be monitored for signs of *peripheral* neuropathy or worsening neuropathy and appropriate action taken per protocol guidelines. Study treatment dose and schedule modifications for significant and prolonged neuropathic toxicity and dose-reduction are described in Section 4.3.1.7.

SECTION 3.4.3.7: Hyperglycemia

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other ADCs using the same vc-MMAE platform. *Several patients given both DCDT2980S and DCDS4501A had abnormal fasting blood sugar (FBS) at screening with elevations of glucose following steroid administration prior to rituximab dose.* Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of anti-hyperglycemic medications. *Emerging data suggest that hyperglycemia may occur more commonly in individuals with abnormal FBS values or known diabetes. This is also reported for ADCETRIS® (2013 SmPC and 2013 USPI).*

SECTION 3.4.3.8: Hepatotoxicity

~~Hepatotoxicity is a potential risk of the ADCs. Definitive attribution of hepatotoxicity to the ADCs has not been established. Transient dose related increases in hepatic enzyme levels were observed in rats treated with DCDT2980S and DCDS4501A.~~ Elevations in transaminase and/or bilirubin levels requiring dose modifications *and treatment discontinuations* have been reported in the ongoing clinical studies.

SECTION 3.4.3.9: *Commonly Reported Side Effects*

Other commonly reported side effects of both DCDT2980S or DCDS4501A in the Phase I clinical trials and within this study include fatigue, nausea, decreased appetite, vomiting, hair thinning or loss, joint pains, loss of appetite, diarrhea, muscle aches, constipation, increases in blood glucose, and headaches.

SECTION 3.4.6: *Risks Associated with Obinutuzumab Therapy*

No evidence available at the time of the approval of this protocol indicates that special warnings or precautions are appropriate other than those noted in the Obinutuzumab Investigator's Brochure and as described in the following sections.

SECTION 3.4.6.1: *Infusion-Related Reactions and Hypersensitivity Reactions (including Anaphylaxis)*

The commonly experienced IRRs have been characterized by fever, chills, flushing, nausea, vomiting, hypotension, hypertension, fatigue, and other symptoms.

Respiratory infusion-related symptoms, such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema, have also been reported. These IRRs were mostly mild or moderate (NCI CTCAE v3.0, Grade 1 and 2 events), and <10% of the events were severe (Grade 3 events), occurring predominantly during the first hour of the infusion or shortly after the first infusion had finished. The events resolved with the slowing or interruption of the infusion and supportive care. The incidence and severity of IRRs decreased with subsequent infusions. Extensive tumor burden predominantly localized in the blood circulation (e.g., high peripheral lymphocyte count in patients with CLL) may be a predisposing factor for the development of IRRs.

IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions.

SECTION 3.4.6.2: *Tumor Lysis Syndrome*

TLS has been reported with obinutuzumab administration. Patients with a high tumor burden, including patients with a lymphocyte count ≥25 ×10^9/L, particularly patients with B-cell CLL and MCL, are at increased risk for TLS and severe IRRs. All patients with peripheral blood lymphocyte counts of ≥25 ×10^9/L or bulky adenopathy must receive prophylaxis for TLS prior to the initiation of study treatment. This includes appropriate hydration, consisting of fluid intake of approximately 3 L/day, starting 1–2 days prior to the first dose of obinutuzumab, and administration of allopurinol (300 mg/day orally) or a suitable alternative (i.e., rasburicase) treatment, starting at least 72 hours prior to the first infusion of obinutuzumab (Cycle 1, Day 1). All patients should then be carefully monitored during the initial weeks of treatment. Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts ≥25 ×10^9/L) before the second and subsequent infusions of obinutuzumab should receive continuous TLS prophylaxis with allopurinol or a suitable alternative (i.e., rasburicase) and adequate hydration until the risk is abated, as determined by the investigator.

SECTION 3.4.6.3: *Neutropenia*

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. Use of G-CSF has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G-CSF is allowed for treatment of neutropenia in this study. Primary prophylaxis with G-CSF is recommended according to the American Society of Clinical Oncology (ASCO), European Organisation for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines, namely for patients who are ≥60 years old and/or with co-morbidities (Lyman et al. 2004).

SECTION 3.4.6.4: *Thrombocytopenia*

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in patients treated with obinutuzumab. It seems that the first cycle is the greatest risk of hemorrhage in patients treated with obinutuzumab. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants), may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician.

SECTION 3.4.6.5: *Infection*

On the basis of its anticipated mode of action, resulting in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Infections have been reported in patients receiving obinutuzumab. Therefore, obinutuzumab should not be administered to patients with active severe infections.

A "black-box" warning for obinutuzumab states that reactivation of hepatitis B as well as other serious viral infections (e.g., infections caused by cytomegalovirus, Varicella zoster virus, herpes simplex virus, JC virus, and HCV) that were new, reactivated, or exacerbated have been reported with the B cell–depleting antibody rituximab mainly in patients who had received the drug in combination with chemotherapy or as part of a hematopoietic SCT. The risk of such infections with obinutuzumab is unknown. Particular attention should be given to patients who have previously received significant immunosuppressive treatment, such as high-dose chemotherapy and SCT.

A "black-box" warning for obinutuzumab states that JC viral infection (including fatal) that resulted in PML with destructive infection of oligodendrocytes of the CNS white matter) have been reported in patients treated with anti-CD20 therapies, including rituximab and obinutuzumab.

The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as cortical (e.g., aphasia or visual-spatial disorientation) can occur.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA).

Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the diagnosis and management of PML.

SECTION 3.5: MINIMIZATION OF BIAS

For the~~This is a~~ randomized, non-comparative, open-label *portion of the* study~~.~~ *p*~~P~~atients *were*~~will be~~ randomly allocated to two treatment arms in a 1:1 ratio through use of an Interactive Voice and Web Response System (IXRS). A dynamic stratified randomization scheme *was*~~will be~~ employed to ensure balance in the stratification factors as specified in Section 3.1. *This portion of the study (Arms A and B) is now closed to enrollment.*

SECTION 3.6: ADMINISTRATIVE STRUCTURE

Approximately 40 study centers in the United States, Canada, and Europe will participate in the study to enroll approximately *252*~~120~~ patients. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

SECTION 4.1.1: <u>Inclusion Criteria</u>

Patients must meet the following criteria to be eligible for study entry:

- For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one highly effective form of nonhormonal contraception or two effective forms of nonhormonal contraception, **including at least one method with a failure rate of < 1% per year**, through the course of study treatment and for *≥12 months* ~~at least 3 months~~ after the last dose of DCDT2980S ~~*or,*~~ DCDS4501A ~~*or,*~~ rituximab, *or obinutuzumab* (whichever is later) in women and at least 5 months after the last dose of DCDT2980S ~~*or,*~~ DCDS4501A ~~*or,*~~ rituximab, *or obinutuzumab* (whichever is later) in men

Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S ~~*or,*~~ DCDS4501A ~~*or,*~~ rituximab, *or obinutuzumab* (whichever is later).

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT

As described in Section 3.1.1.2, only select investigator sites that have agreed to participate in the non-randomized *(Cohorts C and D)* portion of the study will enroll patients into these cohorts. Cohorts C and D will be opened sequentially following completion of the randomized portion of the study for patients with FL.

For obinutuzumab-containing cohorts (Cohorts E, G, and H), patients with either relapsed or refractory follicular NHL or relapsed or refractory DLBCL will be enrolled. After the safety run-in stage for DCDS4501A at 1.8 mg/kg in combination with obinutuzumab, the patients will be enrolled into the dose-expansion portion with 40 patients in each histology group.

SECTION 4.3.1.3: Dosage Modification

Specific guidelines around dosage modifications for neutropenia and peripheral neuropathy are detailed below in Sections 4.3.1.6 and 4.3.1.7. Patients who experience other treatment-related Grade 3 or 4 toxicity or laboratory abnormalities will be allowed to delay dosing of study treatment (both ADC and rituximab *or obinutuzumab*) for up to 2 weeks to allow for recovery. Patients may continue to receive additional infusions of DCDT2980S or DCDS4501A per their treatment assignment provided that the toxicity has resolved to Grade $\leq$2 or $\geq$80% of the baseline value, whichever is lower, within the 2–week delay period. Upon resolution, the dose for subsequent infusions may be reduced to 1.8 mg/kg *(in Cohorts C and D)*. If the toxicity that resulted in the dose reduction persists or recurs at the reduced dose, then the patient should be discontinued from study treatment. The decision for dose modification will be made on the basis of the investigator's assessment of ongoing clinical benefit with continued study treatment and in consultation with the Medical Monitor.

Once dose reductions of DCDT2980S or DCDS4501A are made for toxicity, dose re-escalation will not be allowed. Patients who are enrolled in the non-randomized portion of the study (Cohorts C and D), are dosed at an ADC dose of 1.8 mg/kg, and have progressive disease in the absence of any drug-related toxicity may have their ADC dose increased to 2.4 mg/kg if it is felt that there is reasonable justification for ongoing clinical benefit. The decision to increase the dose must be made in consultation with and approval of the Medical Monitor. *Patients in Cohorts E, G, and H (obinutuzumab-containing cohorts) will not be eligible for dose escalation.*

If a patient develops unacceptable toxicity to DCDT2980S or DCDS4501A, requiring its discontinuation, single-agent rituximab may be continued on the basis of the investigator's assessment of ongoing clinical benefit and with the approval of the Medical

Monitor. *Patients enrolled in obinutuzumab-containing cohorts will not continue on single-agent obinutuzumab unless approved by the Medical Monitor.*

SECTION 4.3.1.4: Schedule Modification

Patients in whom toxicities have not resolved to Grade ≤2 or ≥80% of baseline value, whichever is lower, may have their study treatment delayed by up to 2 weeks. Dosing of both DCDT2980S or DCDS4501A and rituximab *or obinutuzumab* should be held during this period. If all study drug–related toxicities have resolved sufficiently, the patient may resume DCDT2980S or DCDS4501A and rituximab *or obinutuzumab* dosing on the regular every-21-day schedule.

SECTION 4.3.1.6: Neutropenia

Because neutropenia is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.2.3), the use of growth factor support (G-CSF) as prophylactic and therapeutic indications is permitted (see Appendix F) in order to allow continued dosing of DCDT2980S/DCDS4501A. Dose modifications for patients who experience treatment-related Grade 3–4 neutropenia in the context of G-CSF usage are as follows:

- Patients who experience treatment-related Grade 3–4 neutropenia will be allowed to delay dosing of study treatment (both ADC and rituximab *or obinutuzumab*) for up to two weeks to allow for recovery. Therapeutic G-CSF is permitted as clinically indicated (see Appendix F) and to facilitate neutrophil recovery to allow subsequent DCDT2980S/DCDS4501A dosing.
- Subsequent dosing of DCDT2980S/DCDS4501A *and rituximab/obinutuzumab* is permitted provided that the neutropenia has resolved to Grade ≤2 or ≥80% of the baseline value, whichever is lower, within the 2-week period.
- If prophylactic G-CSF was not administered prior to the cycle in which the Grade 3–4 neutropenia developed, then prophylactic G-CSF may be administered prior to subsequent cycles without DCDT2980S/DCDS4501A dose reduction. The dose schedule may be changed from 21-day to 28-day cycles to provide sufficient time for neutrophil recovery in subsequent cycles. In the absence of prophylactic G-CSF or dose schedule modification, the dose of DCDT2980S/DCDS4501A in subsequent cycles should be reduced to 1.8 mg/kg. *For Cohorts E, G, and H, patients will be given DCDS4501A at a dose of 1.8 mg/kg, and further dose reductions cannot be made.*
- For patients enrolled into the non-randomized portion of the study (Cohorts C and D*, as well as Cohorts E, G, and H*), dose modifications will not be allowed. Administration of therapeutic/prophylactic G-CSF and dose-schedule modifications as described above are allowed. Patients who have persistent or recurrent Grade 3–4 neutropenia as defined above should be discontinued from study treatment.

SECTION 4.3.1.7: Peripheral Sensory*/Motor* Neuropathy

Peripheral ~~sensory~~ neuropathy *(sensory or motor)* is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.2.5). For new or worsening drug-related Grade 2 or 3

peripheral sensory *and/or motor* neuropathy, dosing should be held for up to 2 weeks until peripheral ~~sensory~~ neuropathy *(sensory or motor)* improves to Grade 1 or baseline grade. Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and approval of the Medical Monitor based on an assessment of the benefit-risk analysis of continuing to delay study treatment.

Following resolution of peripheral ~~sensory~~ neuropathy *(sensory and/or motor)*, subsequent doses of DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg. *DCDS4501A should not be reduced to a dose lower than 1.8 mg/kg.* If worsening Grade 2 or 3 peripheral ~~sensory~~ neuropathy *(sensory and/or motor)* recurs following dose reduction, study treatment should be discontinued. For Grade *3*~~4~~ peripheral ~~sensory~~ neuropathy *(sensory and/or motor)*, study treatment should be discontinued.

For patients enrolled into the non-randomized portion of the study (Cohorts C and D), dose modifications will not be allowed. Patients who have Grade 2 or 3 peripheral ~~sensory~~ neuropathy *(sensory and/or motor),* as defined above*,* should be discontinued from study treatment.

SECTION 4.3.3: *Obinutuzumab*

SECTION 4.3.3.1: *Formulation*

Obinutuzumab (GA101/Gazyva™/Gazyvaro) is a clear, colorless to slightly brownish liquid, provided as a single 1000-mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50–mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188, and highly purified water (HPW).

SECTION 4.3.3.2: *Dosage, Administration and Storage*

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg in combination with DCDS4501A, as outlined in Section 3.1.3. Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–8 (see Table 2). No dose modifications of obinutuzumab are allowed.

All obinutuzumab infusions should be administered after premedication with oral acetaminophen and an antihistamine (see Section 4.4.1). The prophylactic use of corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) may also be considered for patients thought to be at high risk for IRRs, if deemed appropriate by the investigator, and should be administered prior to the obinutuzumab infusion. On Cycle 1 Day 1, it is recommended that oral prednisone, prednisolone, or methylprednisolone be given within 12 hours as a premedication but at least 60 minutes prior to the obinutuzumab infusion. Premedication with prednisone or prednisolone is mandatory in patients who had an IRR and should continue until IRRs no longer occur during antibody infusion. For the management of IRRs and anaphylaxis, see Table 1 (Section 4.3.1.5).

If it is the strong preference of the investigator or of the site (e.g., for logistical reasons) or if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count), the administration of obinutuzumab infusion can be split over 2 days.

In all parts of the study, obinutuzumab must be administered in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available, and patients should be under the close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Table 1 (Section 4.3.1.5).

Obinutuzumab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. Administration sets with PVC, polyurethane (PUR), or PE as a product contact surface and IV bags with polyolefin (PO), polypropylene (PP), PVC, or PE as a product contact surface are compatible and can be used. Do not use an additional in-line filter because of potential adsorption.

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For clinical formulation-specific and batch-specific instructions and information on in-use stability, see the packaging label.

SECTION 4.3.3.3: *Dosage Modification*

There will be no obinutuzumab dose modification in this study. Patients at high risk for TLS complications (see Section 3.4.2.2) may, at the investigator's discretion, receive obinutuzumab over 2 consecutive days (with DCDS4501A dose potentially delayed to Day 2 or Day 3).

Any NCI CTCAE (v4.0) toxicity Grade ≥3 in severity that is deemed related to obinutuzumab treatment will require interruption of study treatment (both DCDS4501A and obinutuzumab) until resolution to Grade ≤2 or ≥80% of baseline, whichever is lower. Resumption of obinutuzumab treatment may be considered in patients with resolution of toxicities to Grade ≤1 within 2 weeks at the discretion of the investigator, after consultation with the Medical Monitor. Failure of such toxicities to resolve after 2-week delay in study treatment will require permanent discontinuation of obinutuzumab. Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and approval of the Medical Monitor based on an assessment of the benefit-risk analysis of continuing to delay study treatment.

If a patient develops unacceptable toxicity to obinutuzumab requiring its discontinuation, single-agent DCDS4501A will not be permitted.

SECTION 4.3.3.4: *Schedule Modification*

Patients in whom toxicities have not resolved (i.e., to Grade ≤1 or ≥80% of baseline) may have their study treatment delayed by up to 2 weeks. ***Dosing of both DCDS4501A***

and obinutuzumab should be held during this period. *If all study drug–related toxicities have resolved to Grade ≤1 or ≥ 80% of baseline, the patient may resume DCDS4501A and obinutuzumab dosing on the regular every–21–day schedule. In addition, a patient's dosing may be changed to a 28-day cycle if it is felt by the investigator and Medical Monitor that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from transient cytopenias without requiring repeated treatment delays.*

Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.6). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

Specific guidelines around schedule modifications for thrombocytopenia are detailed below in Section 4.3.3.5.

SECTION 4.3.3.5: *Thrombocytopenia*

Thrombocytopenia is a known risk of obinutuzumab (see Section 3.4.5.4). If the clinical condition of a patient requires the use of concomitant anticoagulants, the patient is at increased risk of bleeding when the platelet count is <20,000/μL. When possible, replace prior therapy with Vitamin K antagonists, such as warfarin, with low-molecular weight heparin (LMWH) or new oral anticoagulants (NOACs) before Cycle 1 Day 1. Clinical decision making may be adjusted depending on the patient-specific assessment of benefit and risk.

In the event of severe thrombocytopenia (platelet count <10,000/μL) and/or symptomatic bleeding (irrespective of platelet count) in patients who are not receiving concomitant anticoagulants or platelet inhibitors:

- *Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves, but do not skip any doses of obinutuzumab for the sake of maintaining the study treatment schedule.*

In the event of thrombocytopenia with platelet count <20,000/μL and/or symptomatic bleeding (irrespective of platelet count) in patients who are receiving concomitant anticoagulants or platelet inhibitors:

- *Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves, but do not skip any doses of obinutuzumab for the sake of maintaining the study treatment schedule.*
- *For patients who are on LMWH or NOACs, when platelet count <20,000/μL develops, reduce the dose of LMWH or NOACs used.*

- *For patients who are on platelet inhibitors when thrombocytopenia with platelet count <20,000/μL develops, consideration should be given to temporarily pausing the use of platelet inhibitors.*

SECTION 4.3.4: *Investigational Medicinal Product Accountability*

All investigational medicinal products (IMPs) required for completion of this study (pinatuzumab vedotin [DCDT2980S], polatuzumab vedotin [DCDS4501A], rituximab, and obinutuzumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will be either disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

SECTION 4.4.1: Concomitant Therapy

Concomitant therapy includes any *medication (e.g.,* prescription *drugs,* ~~medications or~~ over-the-counter *drugs, herbal or homeopathic remedies, and nutritional supplements)* ~~preparations~~ used by a patient *from*~~between the~~ 7 days *prior to*~~preceding~~ the screening evaluation ~~and~~ *to* the end of study visits. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF). Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Concomitant use of hematopoietic growth factors is allowed in accordance with instructions provided in the package inserts.

For patients enrolled on obinutuzumab-containing regimens, it is recommended that oral prednisone, prednisolone, or methylprednisolone be given as premedication within 12 hours of, but at least 60 minutes prior to, the obinutuzumab infusion on Cycle 1 Day 1. After the first obinutuzumab infusion, additional glucocorticoids are allowed at the investigator's discretion. For patients who did not experience infusion-related symptoms with their previous infusion, premedication at subsequent infusions may be omitted at the investigator's discretion.

SECTION 4.4.2: Excluded Therapy

Patients who require the use of any of these agents will be discontinued from all study treatment. Patients who are discontinued from study treatment will be followed for safety outcomes for 30 days following the patient's last dose of DCDT2980S or DCDS4501A or rituximab *or obinutuzumab*, whichever is later, or until the patient receives another anti-cancer therapy, whichever occurs first.

SECTION 4.5.1.2: Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure while the patient is in a sitting or semi-supine position, pulse oximetry, pulse rate, and body temperature. Every effort will be made to ensure that vital signs are obtained from patients in a consistent manner and position. The timing of vital sign collection on the days of study treatment administration is as follows:

- For the administration of rituximab *or obinutuzumab*, vital signs should be assessed prior to the start of the infusion, every 15 (±5) minutes during the first hour of the infusion, as clinically indicated during the remainder of the infusion, and following the completion of the infusion.

SECTION 4.5.1.3: Physical Examination

Resolution or any change in grade of peripheral neuropathy AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV). This also applies to AEs for which study drug was discontinued or for patients in the follow-up phase after last dose of study treatment with either ongoing AEs or new onset of an AE. For the AEs referring to the follow-up phase newly initiated, relevant treatments need to be documented with treatment dates.

SECTION 4.5.1.4: Laboratory Assessments
Central Laboratory Assessments

Samples for flow cytometry, PK, bone marrow, and anti-DCDT2980S ~~or~~, anti-DCDS4501A, *or anti-obinutuzumab* antibody assessments will be sent to one or several laboratories or to Genentech for analyses (see Section 3.6). The following assessments will be conducted:

- ATA assays

  ATAs to DCDT2980S ~~or~~, DCDS4501A, *or obinutuzumab* will be determined at Genentech using a validated ELISA (see Section 4.9).

- PK *and PD* assays (see Section 4.5.1.6)
- A plasma sample *and blood samples* will be collected from patients for exploratory research as indicated in Section 4.5.1.9

SECTION 4.5.1.5: Electrocardiogram Assessments

Twelve-lead digital ECG measurements will be obtained in triplicate, with immediately consecutive ECGs obtained until three evaluable ECGs are recorded, at the following timepoints:

- Day 8 (±1 day) of Cycle 3 time matched (i.e., obtained at the same time of day) with post-DCDT2980s/DCDS4501A infusion ECGs for Cycle 3 *only for rituximab-containing arms/cohorts*

SECTION 4.5.1.6: Pharmacokinetic *and Pharmacodynamic* Assessments

Pharmacokinetics of DCDT2980S and DCDS4501A will be characterized by measuring total antibody (conjugated and unconjugated antibody), acMMAE, and free MMAE

concentrations using validated methods (see Section 4.9). Plasma samples may also be analyzed for other potential MMAE-containing catabolites, per sponsor's discretion. Pharmacokinetics of rituximab will be characterized by measuring rituximab concentrations using a validated method (see Section 4.9). *Pharmacokinetics of obinutuzumab will be characterized by measuring obinutuzumab concentrations with use of a validated method (see Section 4.9).* These assessments will allow for further characterization of pharmacokinetics of DCDT2980S and DCDS4501A, the assessment of the drug interaction potential when they are given in combination with rituximab *or obinutuzumab*, and the investigation of potential correlations between PK parameters and safety and/or activity if data allow and at the sponsor's discretion. *Pharmacodynamics of obinutuzumab and DCS4501A may be assessed by monitoring the release of tumor associated DNA following treatment.*

SECTION 4.5.1.7: Immunogenicity Assessments

The schedule of sample collection for ATA assessment is outlined in Appendices B-1*,* ~~and~~ B-2*, or B-3*, depending on the schedule of study treatment administration. Samples for ATA will not be collected during the crossover treatment period.

ATA responses to obinutuzumab will be detected and confirmed using a similar tiered approach. Patient samples will first be screened to detect all antibody responses to obinutuzumab. Samples that screen positive will be analyzed in a confirmatory assay (competitive binding with obinutuzumab) to assess the specificity of the positive response. The relative levels of ATA in confirmed positive samples will be determined in a titering assay. Positive ATA samples will be stored for further characterization of ATA responses, if necessary.

SECTION 4.5.1.8: Tumor Response Assessments

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, on the basis of physical examinations, CT *scans, PET scans,* and/or MRI scans, and bone marrow examinations, using standard response criteria for NHL (Cheson et al. 2007) (see Appendix C-*1 and C-2*).

a. Radiographic Assessments *for Patients on Rituximab-Containing Arms/Cohorts*

b. *Radiographic Assessments for Patients on Obinutuzumab-Containing Cohorts*

PET scans should minimally extend from skull-base to mid-thigh. Full-body PET scan should be performed when clinically appropriate.

CT scans with oral and IV contrast should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated. CT scans for response assessment may be limited to areas of prior involvement only if required by local health

authorities. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

In patients for whom contrast is contraindicated—for example, patients with contrast allergy or impaired renal CL—CT or combined PET/CT scans without contrast are permitted so long as they permit consistent and precise measurement of target lesions during the study treatment period.

PET and CT scans are required for follicular NHL and DLBCL patients at screening, after Cycle 4 of study treatment (i.e., between Cycle 4 Day 15 and Cycle 5 Day 1), and at EOT. The EOT response assessment should be performed 6–8 weeks after Cycle 8 Day 1 or last study treatment. CT scans without PET scans will be obtained every 3 months for 1 year, then every 6 months for 1 year, for a total of approximately 2 years after the treatment completion visit, with use of standard response criteria for NHL (see Appendix C-2).

~~c~~*d*. Schedule of Tumor Response Assessments *for Rituximab-Containing Arms/Cohorts*

Tumor response assessments will be performed every 3 months (±1 week) from the initiation of study treatment until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). The schedule of tumor assessments *is*~~should be~~ independent of the study treatment dose schedule. *For patients enrolled on rituximab-containing arms/cohorts,* the schedule of tumor response assessments is detailed in Appendix A-1. As stated above, for all DLBCL patients *enrolled on a rituximab-containing arm/cohort*, PET scans are required during the screening period and at the 6-month tumor assessment timepoint.

Additional response assessments, after the final dose of study treatment, for patients who discontinue from study treatment (either initial or crossover treatment) for reasons other than progressive disease, will be performed as described in Appendix A-~~ 3~~4.

e. Schedule of Tumor Response Assessments for Obinutuzumab-Containing Cohorts

All follicular NHL and DLBCL patients enrolled in obinutuzumab-containing cohorts are required to have a combined PET and CT scan at screening, after Cycle 4 of treatment, and at EOT. The schedule for tumor response assessments for patients enrolled on obinutuzumab-containing cohorts is detailed in Appendix A-3.

SECTION 4.5.1.9: Exploratory Research

a. Tumor Tissue Samples

Required Tumor Tissue Samples

- Tissue microarrays (TMAs) from cores taken from provided blocks for immunohistochemistry (IHC) and in situ hybridization (ISH) assessments ~~, including~~

~~1) DLBCL classifiers in tissue obtained from patients with DLBCL (CD10; GCET, Mum1; FoxP1 LMO2 (Meyer et al. 2011); and 2)~~*for* biomarker endpoints involved in response to chemotherapy including quantitation of Bcl-2 protein and genetic alterations of bcl-2 including gene rearrangements, amplifications, and t(14;18) translocations. Additional IHC markers may include those related to the tumor microenvironment.

b. Blood and Plasma Samples

Blood samples will be taken aligned with PK sampling to assess the pharmacodynamics response by monitoring circulating tumor DNA.

The plasma and blood samples may be used for the assessment of specific tumor biologic markers, including proteins, circulating DNA, and microRNAs. The information obtained from these samples will enable a better understanding of the biology of NHL and disease prognosis, identify potential predictors of response to treatment with DCDT2980S, DCDS4501A, ~~and/or~~ rituximab, *and/or obinutuzumab*, improve diagnostic assessments, and identify and characterize mechanisms of resistance to DCDT2980S or DCDS4501A and rituximab *or obinutuzumab* activity.

SECTION 4.5.1.10: Patient-Reported Outcome*s*

The MDASI (Cleeland et al., 2000; Appendix E) is a multi-symptom ~~PRO~~*self-report* measure for clinical and research use. The MDASI's 13 core-symptom items, plus an additional 4 items, for a total of 17 symptom items, include those found to have the highest frequency and/or severity in patients with various cancers and treatment types. These include pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling. Six additional items focus on the degree of interference of the aforementioned symptoms for a total of 23 items in the questionnaire.

SECTION 4.5.2: Screening and Pretreatment Assessments

Refer to the Study Flowchart provided in Appendix A-1 *and A-3* for the schedule of screening and pretreatment assessments.

SECTION 4.5.3: Assessments during Treatment

Study drug infusions (rituximab*, obinutuzumab*, DCDT2980S, or DCDS4501A) should occur on the scheduled 21-day (or 28-day) cycle but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ±1 day from the scheduled date, unless otherwise noted. Study visits starting in Cycle 3 should occur within ±2 days from the scheduled date, unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed prior to study drug infusion unless otherwise noted.

Refer to the Study Flowchart provided in Appendix A-1 for the schedule of treatment period assessments. *For patients enrolled in the obinutuzumab-containing cohorts, refer to the Study Flowchart provided in Appendix A-3.*

SECTION 4.5.4: Study Treatment Completion Visit

Patients who complete study treatment ~~(approximately 1 year/17 cycles)~~ or discontinue from study treatment early will be asked to return to the clinic within 30 days after the last DCDT2980S ~~or~~, DCDS4501A ~~or~~, rituximab, *or obinutuzumab* infusion (whichever is later) for a study treatment completion visit. The visit at which response assessment shows progressive disease may be used as the early termination visit.

Refer to the Study Flowchart provided in Appendix A-1 for assessments to be performed at the treatment completion/early termination visit. *For patients enrolled on the obinutuzumab-containing cohorts, refer to the Study Flowchart provided in Appendix A-3.*

SECTION 4.5.6: Follow-Up Assessments

Ongoing adverse events thought to be related to DCDT2980S, DCS4501A, ~~or~~ rituximab, *or obinutuzumab* will be followed until the event has resolved to baseline (pre-treatment) grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the adverse event.

SECTION 4.5.6.1: *Follow-Up Assessments for Rituximab-Containing Regimens*

Patients who discontinue from study treatment (either initial study treatment or crossover treatment) for reasons other than progressive disease will be followed for response for up to 1 year after the last infusion of study treatment or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Response assessments should occur approximately every 2–3 months following the last infusions of DCDT2980S, DCDS4501A, or rituximab. Post-treatment assessments are described in Appendix A-~~3~~4.

SECTION 4.5.6.2: *Follow-Up Assessments for Obinutuzumab-Containing Regimens*

Patients who discontinue from study treatment for reasons other than progressive disease will be followed for response for up to 2 years after the last infusion of study treatment or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Response assessments should occur approximately every 2–3 months following the last infusions of DCDS4501A or obinutuzumab for the first year after completion of treatment, then every 6 months for the second year after completion of treatment. Post-treatment assessments are described in Appendix A-5.

Following discontinuation of study treatment, patients will be followed for survival approximately every 6 months until death, loss to follow-up, withdrawal of consent, or study termination.

SECTION 4.8: POST-TRIAL ACCESS

Genentech does not have any plans to provide DCDT2980S, DCDS4501A, rituximab*, obinutuzumab*, or other study interventions to patients after the conclusion of the study or if the study is terminated or for patients who withdraw early from the study or complete their study treatment. Genentech will evaluate the appropriateness of continuing to provide DCDT2980S, DCDS4501A, ~~or~~ rituximab, *or obinutuzumab* to study patients after evaluating the safety and activity data from the study.

SECTION 4.9.5: *Obinutuzumab ELISA*

Obinutuzumab will be measured in serum samples using a validated ELISA.

SECTION 4.9.6: Anti-Therapeutic Antibody

ATAs against obinutuzumab in serum samples will be measured using a validated bridging antibody ELISA.

SECTION 4.9.7: Biomarker Assays

Tumor tissue assessment of biomarkers will be assayed using IHC, ISH, qPCR gene expression profiling using microarray *and* mutation detection assays. ~~and flow cytometry.~~ *Circulating Tumor DNA (ctDNA) in plasma samples will be assessed using a next generation sequencing approach (CAPP-Seq) to detect and quantitate lymphoma specific markers (Newman et al. 2014).*

SECTION 4.10: STATISTICAL METHODS

The final analysis will be based on patient data collected ~~through patient discontinuation~~ *until all patients discontinue* ~~or~~ *from the* study ~~discontinuation~~ *or the study is terminated by the Sponsor*, whichever occurs first. The analyses will be based on the safety evaluable population, defined as patients who received at least one dose of study treatment. All summaries will be presented according to the disease-specific cohort, treatment group, and assigned dose level.

SECTION 4.10.1: Analysis of the Conduct of the Study

Study drug administration data will be listed by the disease-specific cohorts described in Sections 3.1.1 and 3.1.2. Any dose modifications will be flagged. Means and standard deviations will be used to summarize the total doses of DCDT2980S, DCDS4501A ~~and~~*,* rituximab, *and obinutuzumab* received. All summaries will be presented by treatment group, assigned dose level, and disease-specific cohort.

SECTION 4.10.2: Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, and changes in vital signs. All patients who receive any amount of DCDT2980S, DCDS4501A ~~or~~*,* rituximab,

or obinutuzumab will be included in the safety analysis and will be assigned to the treatment group on the basis of the study treatment received. Patients who have dose level changes from the initial assigned dose level will be summarized by the initial assigned dose level of DCDT2980S or DCDS4501A.

SECTION 4.10.3: Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum concentrations of total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) and rituximab *or obinutuzumab* and plasma concentrations of acMMAE and free MMAE versus time data will be tabulated and plotted by NHL disease subtype (relapsed or refractory follicular NHL or DLBCL). The pharmacokinetics of the above analytes will be summarized by estimating the appropriate PK parameters (e.g., AUC, C_{max}, CL, V_{ss}, and $t_{1/2}$). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and range). Non-compartmental, compartmental, and/or population methods will be used, as data allow.

SECTION 4.10.4: Activity Analyses

ORR from the initial study treatment will be calculated on the basis of data from patients who received study treatment~~ and had at least one post baseline response assessment~~. Objective response is defined as CR or PR as determined by the investigator, on the basis of physical examinations, radiographic scans, and bone marrow examinations, using modified response criteria for NHL (Cheson et al. 2007; see Appendix C) and confirmed by repeat assessments ≥4 weeks after initial documentation. Any patient with insufficient data to determine response will be classified as a non-responder.

For patients with DLBCL, primary assessment of tumor response will be based on diagnostic imaging scans—for example, CT and/or MRI scans and PET scans. For patients with FL *enrolled on rituximab-containing arms/cohorts*, primary assessment of response will be based on CT scans only; the assessment of response in FL based on PET scans will be performed for exploratory purposes only.

For patients with DLBCL or FL on obinutuzumab-containing cohorts, primary assessment of tumor response will be based on PET/CT scans. Given the new Lugano Classification, 2014, criteria which recommend that complete response (PET-CR) be determined by PET-CT scan, patients in Cohorts E, G, and H will be evaluated with a PET-CT scan at screening, between Cycle 4 Day 15 and Cycle 5 Day 1, and at 6-8 weeks after completing treatment. The efficacy analysis for these cohorts will, therefore, be different from the analysis for Arms A-B and Cohorts C-D. (Cheson, et al 2014) (see Appendix C-2).

Among patients with an objective response, duration of response will be defined as the time from the initial *documentation of a* CR or PR to the time of disease progression or death. If a patient does not experience death or disease progression before the end of the study, duration of response will be censored at the day of the last tumor assessment.

For the randomized portion of the study (Arms A and B), PFS is defined as the time from the date of randomization to the date of disease progression or death from any cause, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the ~~day~~ *date* of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. For the non-randomized portion of the study (Cohorts C ~~*and D*~~*through H*), PFS is defined as the time from the date of study enrollment to the date of disease progression or death from any cause, whichever occurs first.

For the randomized portion of the study (Arms A and B), OS is defined as the time from the date of randomization to the date of death from any cause. For the non-randomized portion of the study (Cohorts C ~~*and D*~~*through H*), OS is defined as the time from the date of study enrollment to date of death from any cause.

SECTION 4.10.7: Determination of Sample Size

For the randomized portion of the study (Arms A and B), a target of 120 patients will be enrolled in two separate cohorts of patients (40 in the follicular NHL cohort and 80 in the DLBCL cohort). ~~Genentech has judged this~~*The randomized portion of this study is non-comparative in nature. No formal hypothesis testing is planned to compare the treatment arms. Moreover, there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms. Genentech has judged the proposed* sample size to provide sufficient precision in estimating the anti-tumor activity of DCDT2980S combined with rituximab or DCDS4501A combined with rituximab as measured by objective response. For example, with the assumption of an observed response rate of 40%, a 90% confidence interval for the response rate would be approximately 22%–58% (i.e., 40% ± 18%) for the follicular NHL cohort and approximately 27%–53% (i.e., 40% ± 13%) for the DLBCL cohort. *With 40 patients, there is an 87% chance of observing at least one adverse event with a true incidence of 5%.*

~~This is a non-comparative hypothesis-generating study. There is no formal hypothesis testing planned to compare the treatment arms.~~ ~~*Specifically, for the randomized portion of the study,*~~ ~~there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms.~~*For the non-randomized portions of the study (Cohorts C and D), approximately 20 patients will be enrolled into each arm, for a total of 40 patients. With 20 patients under an observed response rate of 40%, the exact Clopper-Pearson 90% confidence interval for the response rate would be 22%–61%. With respect to the assessment of safety based upon a sample size of 20 patients, the chance of observing at least one adverse event with a true incidence of 10% is 88%.*

For the obinutuzumab safety run-in cohort (Cohort E), 6 patients will be enrolled. For the obinutuzumab expansion cohorts (Cohorts G and H), 40 patients with follicular NHL and the other with 20–40 patients with DLBCL, will be enrolled at the RP2D to further evaluate safety and efficacy of the combination. Table 3 provides asymptotic 90% confidence intervals for the true probability of response for a range of observed proportions based upon a

sample of 40 patients. A sample size of 40 patients is deemed sufficient to provide adequate precision on the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting rate of 45% assuming observed response rates of approximately 60% or higher (~24 responders observed among 40 patients).

Therefore, up to 252 patients may be enrolled in this study.

SECTION 5.4.1: Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product

Medical Monitor Contact Information for sites in North America:

Medical Monitor: [redacted] M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

SECTION 5.4.2: Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

Sites in North America:

Fax No.: [redacted]

~~Alternate~~

~~Fax No.:~~ [redacted]

~~Sites outside of North America: Refer to the study reference binder for contact information.~~

SECTION 5.6: POST-STUDY ADVERSE EVENTS

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt to be related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to Genentech Drug Safety on the study eCRF. If the study eCRF is no longer available, the investigator should report the event directly to Genentech Drug Safety ~~via phone at~~*either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided below.*

Canada:

Fax No.: (905) 542–5864

Email: mississauga.drug_safety@roche.com ~~888-835-2555.~~

United States:

Fax No.: [redacted]

Email: us_drug.safety@gene.com

SECTION 6.5: STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Genentech representative to inspect *site facilities and equipment,* study *source* data, patients' medical records, and eCRFs. The Principal Investigator will *oversee all aspects of the conduct of this protocol and* permit Genentech monitors/representatives and collaborators, the FDA, other regulatory agencies, Institutional Review Boards, and the respective national or local health authorities to inspect facilities and records relevant to this study.

SECTION 6.5: SOURCE DATA DOCUMENTATION

Source documents are where *original* patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, *certified accurate and complete* copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Original s~~S~~ource documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to *all* applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

FIGURE 3a: Study Schema for Rituximab-Containing Arms/Cohorts

Figure 3a has been revised to reflect changes to the protocol.

FIGURE 3b: *Study Schema for Obinutuzumab-Containing Arms/ Cohorts*

Figure 3b has been added to reflect changes to the protocol.

TABLE 1: Management of Infusion-Related Symptoms *for All Study Drugs*

Table 1 has been revised to reflect changes to the protocol.

TABLE 2: *Administration of First and Subsequent Infusions of Obinutuzumab*

Table 2 has been added. Subsequent tables have been renumbered accordingly.

TABLE 3: *Potential 90% Interval Estimates for the True Response Probability*

Table 3 has been added. Subsequent tables have been renumbered accordingly.

REFERENCES:

The references have been updated to reflect changes to the protocol.

APPENDIX A-1: Study Flowchart: Initial Study Treatment ***(Arms A-B, Cohorts C-D)***

Appendix A-1 has been revised to reflect the changes to the protocol.

APPENDIX A-2: Study Flowchart: Crossover Treatment (Patients Randomized to Arms A or B Only)

Appendix A-2 has been revised to reflect the changes to the protocol.

APPENDIX A-3: ***Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H) : Initial Study Treatment***

Appendix A-3 has been revised to reflect the changes to the protocol.

APPENDIX A-4: Study Flowchart: Post-Treatment Follow-Up ***for Rituximab-Containing Regimens (Arms A-B, Cohorts C-D)***

Appendix A-4 has been revised to reflect changes to the protocol.

APPENDIX A-5: ***Study Flowchart: Post-Treatment Follow-Up for Obinutuzumab-Containing Regimens***

Appendix A-5 has been added.

APPENDIX B-1: Serum and Plasma Pharmacokinetic Schedule for DCDT2980S/DCDS4501A and Rituximab, and ATA Schedule for DCDT2980S/DCDS4501A (For Patients Receiving Rituximab on Day 1 and DCDT2980S/DCDS4501A on Day 2 of Every Cycle)
(Arms A-B, Cohorts C-D)

APPENDIX B-2: Serum and Plasma Pharmacokinetic Schedule for Rituximab and DCDT2980S/DCDS4501A, and ATA Schedule for DCDT2980S/DCDS4501A for Patients Receiving Rituximab and DCDT29808S/DCDS4501A on Day 1 of Every Cycle Beginning Cycle 3
(Arms A-B, Cohorts C-D)

APPENDIX B-3: ***Serum and Plasma Pharmacokinetic, Blood Pharmacodynamic, and ATA Schedule for Obinutuzumab and DCDS4501A (Cohorts E, G-H)***

Appendix B-3 has been added.

APPENDIX C-1: Modified Response and Progression Criteria for NHL

Appendix C has been renamed Appendix C-1.

APPENDIX C-2: ***Revised Criteria for Response Assessment: The Lugano Classification (Cohort E, G-H)***

Appendix C-2 has been added.

APPENDIX D: Anaphylaxis Management

Appendix D has been revised to reflect changes to the protocol.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF *PINATUZUMAB VEDOTIN* (DCDT2980S) IN COMBINATION WITH RITUXIMAB OR *POLATUZUMAB VEDOTIN* (DCDS4501A) IN COMBINATION WITH RITUXIMAB *AND A NON-RANDOMIZED PHASE Ib/II EVALUATION OF POLATUZUMAB VEDOTIN IN COMBINATION WITH OBINUTUZUMAB* IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
EUDRACT NUMBER:	2011–004377–84
STUDY DRUG:	*Pinatuzumab Vedotin* (DCDT2980S); *Polatuzumab Vedotin* (DCDS4501A)
IND:	107713
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return a copy of the form to the CRO Monitor at your site. Please retain the original for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF *PINATUZUMAB VEDOTIN (*DCDT2980S*)* IN COMBINATION WITH RITUXIMAB OR *POLATUZUMAB VEDOTIN (*DCDS4501A*)* IN COMBINATION WITH RITUXIMAB *AND A NON-RANDOMIZED PHASE Ib/II EVALUATION OF POLATUZUMAB VEDOTIN IN COMBINATION WITH OBINUTUZUMAB* IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
VERSION NUMBER:	2
EUDRACT NUMBER:	2011-004377-84
IND:	107713
STUDY DRUG:	*Pinatuzumab Vedotin (*DCDT2980S*)*; *Polatuzumab Vedotin (*DCDS4501A*)*
PHASE:	II
INDICATION:	Relapsed or refractory B-cell NHL
SPONSOR:	Genentech, Inc.

Objectives

Primary Objectives

The primary objectives of this study are the following:

- To assess the safety and tolerability of the combination of DCDT2980S and rituximab administered to patients with relapsed or refractory follicular non-Hodgkin's lymphoma (NHL) and diffuse large B-cell lymphoma (DLBCL)
- To assess the safety and tolerability of the combination of DCDS4501A and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- *To assess the safety and tolerability of the combination of DCDS4501A and obinutuzumab when administered to patients with relapsed or refractory follicular NHL or DLBCL*
- To assess the anti-tumor activity of the combination of DCDT2980S and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- *To assess the anti-tumor activity of the combination of DCDS4501A and obinutuzumab in patients with relapsed or refractory follicular NHL and DLBCL*

The secondary safety objectives of this study are the following:

- To assess the incidence of antibody formation to DCDT2980S, DCDS4501A*, and obinutuzumab as measured by the formation of anti-therapeutic antibodies (ATAs)*
- To compare the safety and tolerability of the combination of DCT2980S and rituximab and DCDS4501A and rituximab *or obinutuzumab*

Activity Objectives

The secondary activity objective of the study is the following:

- To compare the anti-tumor activity of the combination of DCT2980S and rituximab and DCDS4501A and rituximab *or obinutuzumab*

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives of this study are the following:

- To characterize the pharmacokinetics of DCDT2980S and rituximab in patients with relapsed or refractory NHL when the two drugs are given in combination
- To characterize the pharmacokinetics of DCDS4501A and rituximab *or obinutuzumab* in patients with relapsed or refractory NHL when the two drugs are given in combination

Patient-*Reported Outcome Objectives*

The objective of this study related to assessment of *patient-reported outcomes (PRO)* is the following:

- To assess patient-*reported* tolerability to study treatment and the impact of study treatment on patient *functioning,* on the basis of PRO

Biomarker Objectives

The objectives of this study related to assessment of biologic markers are the following:

- To make a preliminary assessment of biologic markers that might act as predictors of DCDT2980S + rituximab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL
- To make a preliminary assessment of biologic markers that might act as predictors of DCDS4501A + rituximab *or obinutuzumab* combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL

Study Design

Description of Study

This is a Phase *Ib/*II, multicenter, open-label study. *Up to approximately 252* patients with relapsed or refractory *FL and* DLBCL will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data. *Arms A and B and Cohort C are no longer enrolling patients.*

For Obinutuzumab Cohorts:

Only investigational sites in the United States will enroll patients into Cohort E. Investigational sites in the United States and Canada will participate in Cohorts G and H).

The study will be composed of a randomized portion and a non-randomized portion, as described in the protocol.

Rituximab-Containing Regimens with DCDT2980S or DCDS4501A

Randomized Portion of the Study (Arms A and B)

Following determination of eligibility, patients within each disease group will be randomized in a 1:1 ratio to receive one of two treatments:

- Arm A: Rituximab (375 mg/m^2) followed by DCDT2980S (2.4 mg/kg) every 21 days;
- Arm B: Rituximab (375 mg/m^2) followed by DCDS4501A (2.4 mg/kg) every 21 days

The first day of treatment constitutes Day 1 of each cycle. A typical cycle is 21 days in duration.

A dynamic hierarchical randomization scheme will be employed with respect to the following stratification factors:

- For patients with follicular lymphoma (FL) (see the protocol for definitions)

  Rituximab refractory disease (no response or disease relapse $<$ 6 months from last rituximab treatment) versus rituximab relapsed disease (disease relapse after response $\geq$ 6 months from last rituximab treatment)

- For patients with DLBCL (see the protocol for definitions)

  Second-line versus third-line (or beyond) therapy

  For second-line patients, disease relapse or no objective response (complete response [CR], unconfirmed CR [CRu], or partial response [PR]) <12 months from the start of initial therapy versus disease relapse, after initial objective response (CR, unconfirmed response [CRu] or PR), $\geq$ 12 months from start of initial therapy

  For third-line patients, failure to achieve a CR or progression < 6 months from start of most recent therapy versus CR or progression ≥ 6 months from start of most recent therapy

No formal testing comparing the two treatment arms in the randomized portion of the study is planned.

Non-Randomized Portion of the Study *with Rituximab* (Cohorts C and D)

Only select investigator sites that have agreed to participate in the non-randomized portion of the study will enroll patients into these cohorts.

Patients with relapsed or refractory follicular NHL will be enrolled in Cohorts C and D to receive rituximab (375 mg/m^2) combined with DCDT2980S or DCDS4501A at a dose of 1.8 mg/kg. The first day of treatment constitutes Day 1 of each cycle. A typical cycle will be 21 days in duration.

The opening of either or both cohorts will be at the Sponsor's discretion and only after the enrollment of patients with FL into the randomized portion of the study is completed. Patients will not be randomized to receive one treatment or the other. It is anticipated that Cohort C and D will be opened sequentially.

All Patients *on Rituximab-Containing Arms/Cohorts*

All patients *on rituximab-containing regimens*, regardless of assigned arm/cohort, will receive DCDT2980S or DCDS4501A and rituximab administered by intravenous (IV) infusion on a 21-day cycle. For the first two cycles, rituximab will be administered by IV infusion on Day 1 and DCDT2980S or DCDS4501A will be administered by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this instance, rituximab will be administered first, followed by DCDT2980S or DCDS4501A. In certain circumstances—for example, infusion-related reactions (IRRs) requiring interruption or slowing of infusion rate—rituximab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDT2980S or DCDS4501A may be administered on Day 2 following completion of the rituximab infusion or on Day 3 of the cycle.

Patients may receive treatments for up to 1 year (17 cycles on an every-21-day schedule) if not discontinued because of significant toxicity, disease progression, or withdrawal from study.

Patients will be evaluated for safety and efficacy according to the Schedules of Assessments outlined in the protocol. Initial response assessments in this study will be performed every 3 months from the initiation of therapy until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). Additional response assessments for patients who proceed to crossover treatment will be performed as described in the protocol; response assessments for patients who discontinue study treatment (both initially assigned treatment and crossover treatment) for reasons other than disease progression will be performed as described in the protocol.

Responses to study treatment will be based on investigator assessments. In addition, tumor assessment data will be transmitted to an Independent Review Facility (IRF) for collection and possible independent review.

Obinutuzumab-Containing Regimens with DCDS4501A (Cohorts E, G, and H)

DCDS4501A at 1.8 mg/kg will be given in combination with obinutuzumab to patients with relapsed or refractory follicular NHL and DLBCL in two stages: (1) safety run-in and (2) expansion.

Study treatment will be given in 21-day cycles for both follicular NHL and DLBCL. Patients will be treated for up to a total of 8 cycles. For the first cycle, obinutuzumab will be administered by IV infusion on Days 1, 8, and 15. DCDS4501A will be given on Day 2 for Cycle 1. In the absence of any infusion-related adverse events, obinutuzumab and DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the second cycle. If obinutuzumab and DCDS4501A are administered on the same day, the study drugs will be given sequentially. Obinutuzumab will be administered first, followed by DCDS4501A. In certain circumstances—for example, IRRs requiring interruption or slowing of infusion rate—obinutuzumab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDS4501A may be administered on Day 2 following completion of the obinutuzumab infusion.

Obinutuzumab-Containing Regimen in Phase Ib: Safety Run-In (Cohort E)

This portion of the study will consist of a safety run-in that will evaluate the safety of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in 6 patients (Cohort E). The safety run-in is described in detail in the protocol. In case an amendment to the protocol allows to study higher doses of DCDS4501A, the safety run-in for the 1.8 mg/kg may be shortened to 3 patients.

Obinutuzumab-Containing Regimens in Phase II: Expansion Stage (Cohorts G and H)

After the safety run-in has demonstrated that DCDS4501A at 1.8 mg/kg in combination with obinutuzumab is safe to administer, patients will be enrolled into two expansion cohorts based on histology of follicular NHL or DLBCL (Cohorts G and H respectively). Forty patients will be enrolled into each expansion cohort. An additional cohort(s) may be added in the future.

Follicular NHL ***Patients for Rituximab-Containing Arms/Cohorts***

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed to regimens containing rituximab, defined as documented history of response (CR, CRu, or PR) of ≥ 6 months in duration from completion of all prior rituximab-containing regimens. A rituximab-containing regimen is defined as rituximab as a single agent during induction and/or maintenance or in combination with other agents during induction and/or maintenance.
- Refractory to any prior regimen containing rituximab, defined as no response to or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:

  Patients with progressive disease while receiving rituximab monotherapy, rituximab combined with chemotherapy, or rituximab maintenance therapy; patients must have received at least one full dose (375 mg/m^2) of rituximab.

  Patients with no objective response (PR or CR) to a rituximab-containing regimen consisting of at least 4 weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

  Patients with disease relapse, after having achieved an objective response, within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Enrollment of patients with refractory disease as defined above may be limited to no greater than 60% of the total follicular NHL cohort, in order to avoid overrepresentation of the refractory disease population.

Follicular NHL Patients for Obinutuzumab-Containing Cohorts

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- *Relapsed to prior regimen(s) after having a documented history of response (CR, CRu, or PR) of ≥6 months in duration from completion of regimen(s)*
- *Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy*

DLBCL ***Patients for Rituximab-Containing Arms/Cohorts***

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/stem cell transplant (SCT) will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) < 12 months from start of initial therapy (second-line refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response ≥ 12 months from start of initial therapy (second-line relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) < 6 months from start of prior therapy (third-line + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response ≥ 6 months from start of prior therapy (third-line + relapsed)

Enrollment into any of the above four categories may be limited to no greater than 40% of the DLBCL cohort—and to no more than 60% of the two refractory categories combined—in order to avoid overrepresentation of any specific subpopulation, refractory patients in particular.

DLBCL Patients for Obinutuzumab-Containing Cohorts

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/SCT as determined by the investigator will be enrolled into the study as defined by the following:

- *Second-line SCT-ineligible patients with progressive disease or no response (SD) <12 months from start of initial therapy (second-line refractory)*
- *Second-line SCT-ineligible patients with disease relapse after initial response ≥12 months from start of initial therapy (second-line relapsed)*
- *Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) <6 months from start of prior therapy (third-line + refractory)*
- *Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response ≥6 months from start of prior therapy (third-line + relapsed)*

Crossover Treatment (Randomized Patients *in Arms A and B* Only)

Patients randomized to Arm A or Arm B who develop progressive disease may be eligible to receive crossover treatment consisting of rituximab and the other antibody-drug conjugate (ADC) or the other ADC alone—for example, Arm B treatment for patients who have disease progression while receiving Arm A treatment, and vice versa—provided the following conditions are met:

- Patients must not have experienced a toxicity requiring the discontinuation of DCDT2980S/DCDS4501A treatment OR experienced toxicity during the last dose of study treatment that would preclude treatment with the crossover regimen.

  Patients who had modifications to dosing and/or schedule on the initial study treatment will be permitted to receive crossover treatment in the absence of toxicities on the modified dose and/or schedule. The dose and schedule of crossover treatment will be determined by the investigator and the Medical Monitor.

  Patients who had rituximab discontinued and continued on single-agent DCDT2980S/DCDS4501A treatment may receive crossover treatment of single-agent DCDS4501A/ DCDT2980S.

- Patients must have radiographically documented disease progression.
- Patients must meet all inclusion and exclusion criteria described in the Inclusion Criteria and Exclusion Criteria sections below, except for those related to prior rituximab treatment.
- Acceptable toxicity: All study drug–related adverse events from the initial study treatment must have decreased to Grade 1 or baseline grade on or before the first day of treatment on the crossover regimen. Exceptions may be allowed after a careful assessment and discussion of the benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.
- Administration of crossover treatment must be in the best interests of the patient as determined after a careful assessment and discussion of benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.
- A tumor biopsy (described in the protocol) will be required for patients with safely accessible site of disease, defined as requiring only local anesthesia and, in general, excluding the brain, lungs or any internal organs that may subject patients to significant risk.

    Patients for whom a safely accessible site of disease is not present may still receive crossover treatment without undergoing a biopsy. Eligibility to receive crossover treatment should be discussed with and approved by the Medical Monitor.

    A tumor biopsy of a safely accessible site of disease is optional for patients who are not eligible for study cross over.

Patients who are determined to be eligible for study cross over will be treated as follows:

- Assessments obtained at the initial study treatment discontinuation visit (described in the protocol) may be used as screening assessments for crossover treatment. The following re-screening assessments must be repeated/obtained within 1 week prior to starting treatment on the crossover regimen, in order to re-establish baseline pretreatment clinical and disease status: targeted physical exam, Eastern Cooperative Oncology Group (ECOG) status, and hematology and serum chemistry laboratory tests.

    Re-screening tests for hepatitis B and C do not need to be performed unless there is clinical suspicion of hepatitis B and/or C positivity.

    A radiographic tumor assessment must also be performed, unless already done to document disease progression, within 6 weeks prior to starting crossover treatment.
- Crossover treatment will begin no later than 42 days after the last dose of the prior study treatment.

Patients will be treated with the crossover treatment until a second disease progression event relative to the tumor assessment, documenting progressive disease on the initial study treatment, clinical deterioration, and/or intolerance to the crossover treatment for up to a maximum of 1 year (17 cycles on an every-21-day schedule). Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in the protocol. Response assessments for patients who discontinue study treatment for reasons other than disease progression will be performed as described in the protocol.

Clinical data and exploratory data derived from tumor biopsies obtained prior to crossover treatment will be monitored on an ongoing basis. Genentech has the right to restrict or suspend enrollment into crossover treatment at any time. Reasons for this may include, but are not limited to, the following:

- The incidence or severity of adverse events during crossover treatment indicates a potential safety hazard to patients.
- Patient enrollment into crossover treatment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Patients who are enrolled into the non-randomized portion of the study (Cohorts C, D, *E, G, and H*) will not have the option to receive crossover treatment upon disease progression.

Number of Patients

Up to approximately 252 patients with relapsed or refractory *FL and* DLBCL will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form(s)
- Age $\geq$ 18 years
- ECOG Performance Status of 0, 1, or 2
- Life expectancy of at least 12 weeks
- History of histologically documented relapsed or refractory Grades 1–3a FL or relapsed or refractory DLBCL
- Availability of an archival or freshly biopsied tumor tissue sample must be confirmed for study enrollment.
- Have a clinical indication for treatment as determined by the investigator
- Must have at least one bidimensionally measurable lesion ($>$ 1.5 cm in its largest dimension by computed tomography [CT] scan or magnetic resonance imaging [MRI])
- Laboratory values (including patients with hepatic or renal involvement), as follows:

  AST and ALT $\leq 2.5 \times$ ULN

  Total bilirubin $\leq 1.5 \times$ ULN

  Platelet count $\geq$ 75,000/mm^3 (unless thrombocytopenia clearly due to marrow involvement of NHL and/or disease-related immune thrombocytopenia)

  Absolute neutrophil count $\geq$ 1000/mm^3 (without growth factor support, unless neutropenia clearly due to marrow involvement of NHL)

  Total hemoglobin $\geq$ 9 g/dL (without transfusion support $>$ 14 days prior to screening, unless anemia clearly due to marrow involvement of NHL)

  Serum creatinine $\leq$ 2.0 mg/dL or measured creatinine CL $\geq$ 50 mL/min
- For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one highly effective form of nonhormonal contraception or two effective forms of nonhormonal contraception, **including at least one method with a failure rate of < 1% per year**, through the course of study treatment and for *$\geq$ 12 months* after the last dose of DCDT2980S*,* DCDS4501A*,* rituximab, *or obinutuzumab* (whichever is later) in women and at least 5 months after the last dose of DCDT2980S*,* DCDS4501A*,* rituximab, *or obinutuzumab* (whichever is later) in men

  A woman is considered not to be of childbearing potential if she is postmenopausal, defined by amenorrhea of $\geq$ 12 months duration and age $\geq$ 45 years, or has undergone hysterectomy and/or bilateral oophorectomy.

  The following are considered highly effective forms of contraception: 1) true abstinence; 2) male sterilization (with post-procedure documentation of absence of sperm in the ejaculate). For female patients, the sterilized male partner should be the sole partner.

  The following are considered effective forms of contraception: 1) intrauterine device (IUD; copper IUD or hormonal IUDs only) or intrauterine system; 2) condom with spermicidal foam/gel/film/cream/suppository; 3) occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.

  Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S or, DCDS4501A or, rituximab, or obinutuzumab (whichever is later).

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Prior use of any MAb, radioimmunoconjugate or ADC within 4 weeks before Cycle 1, Day 1
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational anti-cancer agent within 2 weeks prior to Cycle 1, Day 1

  Adverse events except for sensory neuropathy from any previous treatments must be resolved or stabilized to Grade ≤ 2 prior to Cycle 1, Day 1.
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1, Day 1
- Prior allogeneic stem cell transplant
- Eligibility for autologous SCT (patients with relapsed or refractory DLBCL)
- History of transformation of indolent disease to DLBCL
- History of severe allergic or anaphylactic reactions to MAb therapy (or recombinant antibody-related fusion proteins)
- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma (e.g., of the cervix or breast) are allowed. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥ 2 years prior to Cycle 1, Day 1.
- Current or past history of CNS lymphoma
- Current Grade > 1 peripheral neuropathy
- Evidence of significant, uncontrolled, concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Recent major surgery within 6 weeks prior to Cycle 1, Day 1, other than for diagnosis
- Presence of positive test results for hepatitis B (HBsAg and/or total anti-HBc) or hepatitis C (HCV antibody)

  Patients who are positive for anti-HBc are eligible only if polymerase chain reaction (PCR) is negative for HBV DNA and it is believed by both the investigator and Medical Monitor that it is in the patient's best interest to participate.

  Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.
- Known history of HIV seropositive status
- Women who are pregnant or lactating
- Ongoing corticosteroid use > 30 mg/day prednisone or equivalent

  Patients receiving corticosteroid treatment ≤ 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy

Length of Study

The length of study will be the time from screening of the first enrolled patient through 2 years after the Treatment Completion Visit for the last enrolled patient on an obinutuzumab-containing regimen. The length of the study for the obinutuzumab-containing cohorts is expected to be approximately 48 months.

End of Study

The end of study is defined as the timepoint at which patients enrolled in the obinutuzumab-containing regimens in the study have had at least 2 years of follow-up from the time of the Treatment Completion Visit or have discontinued from the study.

Outcome Measures

Safety Outcome Measures

The safety and tolerability of the combination of DCDT2980S and rituximab and DCDS4501A and rituximab *or obinutuzumab* will be assessed using the following safety outcome measures:

- Incidence, nature, and severity of adverse events
- Incidence of anti-DCDT2980S*,* anti-DCDS4501A*, or anti-obinutuzumab* antibodies
- Changes in vital signs
- Changes in laboratory values

The determination of the DCDS4501A RP2D in combination with obinutuzumab will be assessed *using the following primary safety outcome measures for the Phase Ib portion of the study:*

- *Incidence and nature of DLTs*
- *Incidence, nature, and severity of adverse events and serious adverse events*
- *Changes in vital signs, physical findings, ECGs, and clinical laboratory values during and following study treatment administration*

Pharmacokinetic/ Pharmacodynamic Outcome Measures

The following PK parameters will be derived from the serum concentration–time profiles of total antibody (the sum of conjugated and unconjugated antibody), including rituximab *or obinutuzumab*, and plasma concentration-time profiles of antibody-conjugated monomethyl auristatin E (acMMAE) and free MMAE following administration of DCDT2980S or DCDS4501A, when appropriate, as data allow:

- Total exposure (area under the concentration-time curve [AUC])
- Maximum plasma and serum concentration (C_{max})
- Clearance (CL)
- Terminal half-life ($t_{1/2}$)
- Steady-state volume of distribution (V_{ss})

Compartmental, non-compartmental, and/or population methods may be used. Other parameters, such as accumulation ratio and trough plasma and serum concentration (C_{min}), may also be calculated.

The following PD outcome measures will be assessed when appropriate, as data allow:

- Peripheral blood B-cell depletion and recovery. For each visit at which $CD19^+$ B-cell measurements are taken, B-cell data will be listed for each patient by dose level as follows:

  Absolute blood cell counts

  Percent change relative to the baseline blood counts

  $CD19^+$ B-cell recovery, defined as the timepoint when the values return to baseline levels or $\geq$50% of baseline levels

Activity Outcome Measures

The following activity outcome measures will be assessed:

- Objective response, defined as a PR or CR
- Duration of objective response, defined as the *duration of time from the* first occurrence of a documented objective response *to* time of relapse or death from any cause

- Progression-free survival (PFS), defined as the *duration from initial* randomization to the first occurrence of progression or death within 30 days of the last administration of study drug, whichever occurs first
- Overall survival (OS), defined as the *duration* from the date of randomization*/enrollment* to the date of death from any cause

Objective response and disease progression will be determined using standard criteria for NHL.

Exploratory Outcome Measures

The exploratory outcome measures will include, but will not be limited to, the following:

- Confirmation and quantitation of CD22, CD79b, and CD20 expression levels in either archival or freshly obtained (when available) tumor specimens (tumor biopsies, bone marrow biopsies, peripheral blood) by immunohistochemistry/flow cytometry/quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)
- Additional assessments related to the understanding of the mechanism of action of DCDT2980S, DCDS4501A, rituximab, *and obinutuzumab*, mechanisms of resistance to DCDT2980S, DCDS4501A*,* rituximab, *and obinutuzumab*, and/or NHL pathogenesis may be included.
- *Treatment and disease symptom* assessments using the M.D. Anderson Symptom Inventory (MDASI)

Investigational Medicinal Products

Test Product

Pinatuzumab Vedotin (DCDT2980S) and Polatuzumab Vedotin (DCDS4501A)

Patients will receive DCDT2980S or DCDS4501A at 1.8 mg/kg or 2.4 mg/kg by IV infusion on Day 1 or Day 2 for each cycle. The total dose of DCDT2980S or DCDS4501A for each patient will be determined by the dose cohort to which the patient is assigned and depend on the patient's weight within 96 hours prior to Day 1 of each cycle.

Rituximab

All patients in rituximab-containing arms/cohorts will receive DCDT2980S or DCDS4501A and rituximab administered by IV infusion on a 21-day cycle. For the first two cycles, patients will receive rituximab 375 mg/m^2 by IV infusion on Day 1 and DCDT2980S or DCDS4501A by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab 375 mg/m^2 and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this case, rituximab will be administered first, followed by DCDT2980S or DCDS4501A.

Obinutuzumab

Patients in obinutuzumab-containing cohorts will receive DCDS4501A and obinutuzumab administered by IV infusion on a 21-day cycle. For the first cycle, patients will receive obinutuzumab 1000 mg by IV infusion on Days 1, 8, and 15. DCDS4501A will be given on Day 2 for Cycle 1. In the absence of any infusion-related adverse events, obinutuzumab and DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the second cycle.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

The final analysis will be based on patient data collected *until all patients discontinue from the* study *or the study is terminated by the Sponsor*, whichever occurs first. The analyses will be based on the safety evaluable population, defined as patients who received at least one dose of study treatment. All summaries will be presented according to the disease-specific cohort, treatment group, and assigned dose level.

Analysis of the Conduct of the Study

Enrollment, major protocol violations, and reasons for discontinuations from the study will be summarized.

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, duration of malignancy, and baseline ECOG Performance Status, will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables. All summaries will be presented overall and by treatment group, assigned dose level, and disease-specific cohort.

Study drug administration data will be listed by the disease-specific cohorts described in the protocol. Any dose modifications will be flagged. Means and standard deviations will be used to summarize the total doses of DCDT2980S, DCDS4501A*,* rituximab, *and obinutuzumab* received. All summaries will be presented by treatment group, assigned dose level, and disease-specific cohort.

Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, and changes in vital signs. All patients who receive any amount of DCDT2980S, DCDS4501A*,* rituximab, *or obinutuzumab* will be included in the safety analysis and will be assigned to the treatment group on the basis of the study treatment received. Patients who have dose level changes from the initial assigned dose level will be summarized by the initial assigned dose level of DCDT2980S or DCDS4501A.

All adverse event data will be listed by study site, patient number, treatment group, disease-specific cohort, and cycle. All adverse events occurring on or after treatment on Day 1 of Cycle 1 will be summarized by mapped terms, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade. In addition, all serious adverse events, including deaths will be listed separately and summarized.

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to DCDT2980S and DCDS4501A will be summarized.

Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum concentrations of total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) and rituximab *or obinutuzumab* and plasma concentrations of acMMAE and free MMAE versus time data will be tabulated and plotted by NHL disease subtype (relapsed or refractory follicular NHL or DLBCL). The pharmacokinetics of the above analytes will be summarized by estimating the appropriate PK parameters (e.g., AUC, C_{max}, CL, V_{ss}, and $t_{1/2}$). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and range). Non-compartmental, compartmental, and/or population methods will be used, as data allow.

Exposure-response (safety and efficacy) analysis may be conducted with use of PK data and available drug effect (e.g., imaging, measures of tumor burden) and toxicity (e.g., clinical pathology) data, at the sponsor's discretion.

In addition, population PK methods may be employed to manage sparse data and to investigate the effects of certain covariates on the pharmacokinetics of DCDT2980S and DCDS4501A, as data allow, and at the sponsor's discretion.

Activity Analyses

Best overall response, duration of response, and PFS will be listed for all patients.

Overall response rate (ORR) from the initial study treatment will be calculated on the basis of data from patients who received study treatment. Objective response is defined as CR or PR as determined by the investigator, on the basis of physical examinations, radiographic scans, and bone marrow examinations, using modified response criteria for NHL and confirmed by repeat assessments $\geq$4 weeks after initial documentation. Any patient with insufficient data to determine response will be classified as a non-responder.

For patients with DLBCL, primary assessment of tumor response will be based on diagnostic imaging scans—for example, CT and/or MRI scans and positron emission tomography (PET) scans. For patients with FL *enrolled on rituximab-containing arms/cohorts*, primary assessment of response will be based on CT scans only; the assessment of response in FL based on PET scans will be performed for exploratory purposes only.

For patients with DLBCL or FL on obinutuzumab-containing cohorts, primary assessment of tumor response will be based on PET/CT scans. Given the new Lugano Classification, 2014, criteria which recommend that complete response (PET-CR) be determined by PET-CT scan, patients in Cohorts E, G, and H will be evaluated with a PET-CT scan at screening, between Cycle 4 Day 15 and Cycle 5 Day 1, and at 6-8 weeks after completing treatment. The efficacy analysis for these cohorts will, therefore, be different from the analysis for Arms A-B and Cohorts C-D. (Cheson, et al 2014) (see Appendix C-2)

Among patients with an objective response, duration of response will be defined as the time from the initial *documentation of a* CR or PR to the time of disease progression or death. If a patient does not experience death or disease progression before the end of the study, duration of response will be censored at the day of the last tumor assessment.

For the randomized portion of the study (Arms A and B), PFS is defined as the time from the date of randomization to the date of disease progression or death from any cause, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the *date* of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. For the non-randomized portion of the study (Cohorts C *through H*), PFS is defined as the time from the date of study enrollment to the date of disease progression or death from any cause, whichever occurs first.

For the randomized portion of the study (Arms A and B), OS is defined as the time from the date of randomization to the date of death from any cause. For the non-randomized portion of the study (Cohorts C *through H*), OS is defined as the time from the date of study enrollment to date of death from any cause.

Exploratory Analyses

Assay results of possible predictive markers will be listed by treatment group and response status.

Summary statistics of the MDASI items, scales, and their changes from baseline will be calculated at each assessment timepoint. The mean, standard error, and median of the absolute scores and the mean changes from baseline (and 95% CI) within and between study arms will be reported for the MDASI scales and single items, as well as the weekly averages of the worst symptom rating. For change scores in the MDASI from baseline, patients without baseline scores will not be included in the analyses. Line charts depicting the means and mean changes of subscales over time will be also provided.

Frequencies and percentages of missing data for the PRO endpoints will be reported. Dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) will be summarized.

Repeated measures mixed-effects models will explore MDASI subscale scores with a baseline score and appropriate covariates added, as appropriate.

Handling of Missing Data

For the endpoint of objective response, patients without a post-baseline tumor assessment will be considered non-responders in the all-treated population analysis.

For duration of response and PFS, data from patients who are lost to follow-up will be included in the analysis as censored observations on the last date that the patient is known to be progression free, defined as the date of the last tumor assessment, or, if no tumor assessments were performed, as the date of last study treatment plus 1 day.

Compliance to PRO data collection will be reported with summary statistics, including frequencies of reasons for non-compliance such as patient refusal to complete PRO data collection.

Determination of Sample Size

For the randomized portion of the study (Arms A and B), a target of 120 patients will be enrolled in two separate cohorts of patients (40 in the follicular NHL cohort and 80 in the DLBCL cohort). *The randomized portion of this study is non-comparative in nature. No formal hypothesis testing is planned to compare the treatment arms. Moreover, there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms. Genentech has judged the proposed* sample size to provide sufficient precision in estimating the anti-tumor activity of DCDT2980S combined with rituximab or DCDS4501A combined with

rituximab as measured by objective response. For example, with the assumption of an observed response rate of 40%, a 90% confidence interval for the response rate would be approximately 22%–58% (i.e., 40% ± 18%) for the follicular NHL cohort and approximately 27%–53% (i.e., 40% ± 13%) for the DLBCL cohort. *With 40 patients, there is an 87% chance of observing at least one adverse event with a true incidence of 5%.*

For the non-randomized portions of the study (Cohorts C and D), approximately 20 patients will be enrolled into each arm, for a total of 40 patients. With 20 patients under an observed response rate of 40%, the exact Clopper-Pearson 90% confidence interval for the response rate would be 22%–61%. With respect to the assessment of safety based upon a sample size of 20 patients, the chance of observing at least one adverse event with a true incidence of 10% is 88%.

For the obinutuzumab safety run-in cohort (Cohort E), 6 patients will be enrolled. For the obinutuzumab expansion cohorts (Cohorts G and H), 40 patients with follicular NHL and 40 patients with DLBCL will be enrolled at the RP2D to further evaluate safety and efficacy of the combination. Table 3 in the protocol provides asymptotic 90% confidence intervals for the true probability of response for a range of observed proportions based upon a sample of 40 patients. A sample size of 40 patients is deemed sufficient to provide adequate precision on the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting rate of 45% assuming observed response rates of approximately 60% or higher (~24 responders observed among 40 patients).

Therefore, up to 252 patients may be enrolled in this study.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ac	antibody-conjugated
ADC	antibody–drug conjugate
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
anti-HBc	hepatitis B core antibody
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from 0 to infinity
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma and serum concentration
C_{min}	trough plasma and serum concentration
CR	complete response
CRu	unconfirmed response
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CVP	cyclophosphamide, vincristine, and prednisone
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC	ethics committee
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
FACS	fluorescence-activated cell sorting

Abbreviation	Definition
FBS	fasting blood sugar
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma
G	GA101 or obinutuzumab
G-CHOP	obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HNSTD	highest non-severely toxic dose
HPW	highly purified water
ICH	International Conference on Harmonisation
IgG1	immunoglobulin-G1
IHC	immunohistochemistry
IL	interleukin
IMC	Internal Monitoring Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
iNHL	indolent non-Hodgkin's lymphoma
IP	interferon-inducible protein
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	infusion-related reaction
ISH	in situ hybridization
IV	intravenous
IXRS	Interactive Voice and Web Response System
JC	John Cunningham
Kd	equilibrium dissociation constant
LC-MS/MS	liquid chromatography–tandem mass spectrometry
LMWH	low-molecular weight heparin
MCL	mantle cell lymphoma
MC-VC-PABC	maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl
MDASI	M.D. Anderson Symptom Inventory
MMAE	monomethyl auristatin E

Abbreviation	Definition
MAb	monoclonal antibody
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NK	natural killer
NOAC	new oral anticoagulant
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PE	polyethylene
PET	positron emission topography
PD	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PP	polypropylene
PR	partial response
PRO	patient-reported outcomes
PVC	polyvinyl chloride
PUR	polyurethane
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
q3w	every 3 weeks
R	rituximab
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RP2D	recommended Phase II dose
SAE	serious adverse event
SC	subcutaneous
SCID	severe combined immunodeficient
SCT	stem cell transplant
SD	stable disease
SDV	source data verification
SmPC	Summary of Product Characteristics

Abbreviation	Definition
STD10	severely toxic dose to 10%
SWFI	Sterile Water for Injection
t1/2	terminal half-life
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
ULN	upper limit of normal
Vss	steady-state volume of distribution

1. BACKGROUND

1.1 BACKGROUND ON DISEASE

B-cell lymphoproliferative disorders are a heterogeneous group of malignancies, ranging from slow-growing indolent and incurable diseases with a median survival of 8–10 years (such as follicular non-Hodgkin's lymphoma [NHL]) to more aggressive intermediate- to high-grade lymphomas (such as diffuse large-cell lymphoma), which can have a median survival of 6 months if left untreated or long-term remission in more than 50% of patients with appropriate treatment. Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL accounting for approximately 30%–40% of all new patients, whereas follicular lymphoma (FL) accounts for approximately 20%–25% of new lymphomas.

Despite advances in the clinical outcomes of patients with NHL using treatments such as the CD20-specific monoclonal antibody (MAb) rituximab (Rituxan®, MabThera®) in combination with chemotherapy, indolent B-cell malignancies remain incurable, as do approximately half of aggressive NHL patients. Thus, there is still a need for treatments that can be combined with chemoimmunotherapy and can significantly extend disease-free and overall survival (OS) in these patients, with at least acceptable, if not superior, safety profiles.

1.2 BACKGROUND ON THE MOLECULES

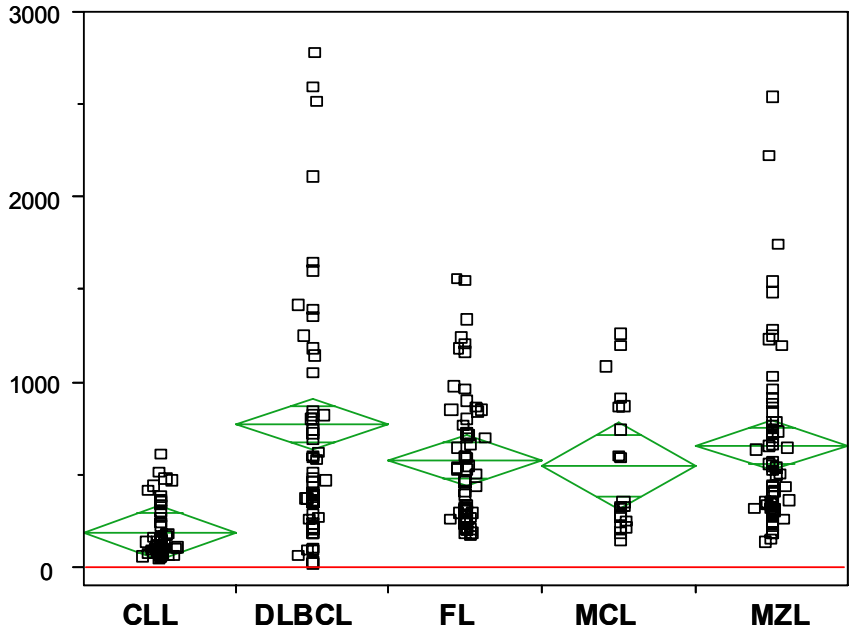
1.2.1 DCDT2980S

1.2.1.1 Background and Preclinical Data

CD22 is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of the B cell–derived malignancies, including nearly all NHL and chronic lymphocytic leukemia (CLL) samples tested (see Figure 1). Antibodies bound to CD22 are rapidly internalized, making CD22 ideally suited for targeted delivery of cytotoxic agents (Shan and Press 1995).

DCDT2980S is an antibody–drug conjugate (ADC) that consists of a potent anti-mitotic agent, monomethyl auristatin E (MMAE) conjugated to a humanized immunoglobulin-G1 (IgG1) anti-CD22 MAb, MCDT2219A, via a protease-labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl (MC-VC-PABC). MMAE has a mode of action similar to vincristine, which is a component of standard chemotherapy used in lymphoma therapy. This therapeutic approach takes advantage of the specific targeting capability of the antibody and the cytotoxic activity of MMAE. Following internalization, the MMAE is deconjugated from DCDT2980S by lysosomal enzymes, binds to tubulin, and disrupts the microtubule network, resulting in inhibition of cell division and cell growth and induction of apoptosis (Doronina et al. 2003).

Figure 1 CD22 Expression Levels on B-Cell Tumor Cells



CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MFI = mean fluorescence intensity; MZL = marginal zone lymphoma.
CD22 expression levels (MFI) on B-cell tumor cells were assessed by flow cytometry in patients diagnosed with the following B-cell lymphomas: CLL (n = 49), DLBCL (n = 59), FL (n = 58), MCL (n = 20), and MZL (n = 60).

Comprehensive pharmacologic, pharmacokinetic (PK), pharmacodynamic (PD), and toxicology evaluations were conducted to support the use of DCDT2980S in clinical trials. DCDT2980S binds human CD22 with a high affinity (equilibrium dissociation constant [K_d] = 1.7 ± 0.2 nM) and showed similar binding affinity to cynomolgus monkey CD22. No binding activity was observed with mouse and rat peripheral blood mononuclear cells (PBMCs).

The unconjugated antibody MCDT2219A did not appear to induce antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) in vitro. In contrast, DCDT2980S displayed potent and selective inhibition of cell proliferation in vitro (50% of the maximal inhibitory concentration [IC_{50}] = 0.33 nM) by cell viability assays. Efficacy studies conducted in murine xenograft models of human lymphoma (CD22-positive WSU-DLCL2 and BJAB cell lines) showed that a single dose of DCDT2980S resulted in regression of tumor growth at doses ranging from 1 to 4 mg/kg. PD studies with DCDT2980S showed that a single dose of 1–6 mg/kg resulted in partial depletion of peripheral blood B cells in cynomolgus monkeys with a corresponding depletion in germinal center B cells in lymphoid tissue.

The PK profiles of DCDT2980S were observed to be linear in rodents and moderately non-linear in cynomolgus monkeys over the tested dose range. The non-linear clearance (CL) observed in cynomolgus monkeys with DCDT2980S is likely due to the contribution of B cell-mediated CL to the total CL. The free MMAE concentrations in cynomolgus monkeys following DCDT2980S administration were generally 10,000 times lower than the concentration of DCDT2980S.

Cynomolgus monkeys were selected as the most relevant nonclinical species for the toxicology and PK/PD studies of DCDT2980S, given the comparable sequence homology of human and cynomolgus monkey CD22, similar binding affinity of DCDT2980S to human and cynomolgus monkey CD22, and comparable tissue cross-reactivity in both human and cynomolgus monkey tissues. DCDT2980S was well tolerated at doses of up to 3 mg/kg (highest non-severely toxic dose [HNSTD]) in monkeys and up to or greater than 10 mg/kg in rats (severely toxic dose to 10% [STD_{10}] of rats $\geq$ 10 mg/kg). Reversible bone marrow toxicity and associated hematopoietic changes were observed in both rats and monkeys treated with DCDT2980S or MMAE, suggesting that the toxicity of DCDT2980S is related to MMAE. Additional effects on liver and lung in rats were minimal in severity and reversible and did not occur in cynomolgus monkeys, which may be due to differences in species sensitivity, exposure, and/or pharmacokinetics.

Complete details of preclinical studies of DCDT2980S can be found in the DCDT2980S Investigator's Brochure.

1.2.1.2 DCDT2980S Clinical Data

a. Patient Enrollment

Both DCDT2980S monotherapy and combination therapy with rituximab have been studied in a Phase I study (Study DCT4862g) of patients with relapsed or refractory B-cell malignancies expected to express CD22, including indolent NHL, DLBCL, mantle cell lymphoma (MCL), and CLL.

All data presented herein is based on a data entry cutoff of 22 February 2013, with clinical data available from 65 patients with NHL (excluding patients with CLL) enrolled in dose-escalation and expansion cohorts. These include 49 patients who were treated with single-agent DCDT2980S at doses ranging from 0.1 to 3.2 mg/kg administered intravenously every 21 days and 16 patients who were enrolled into two Phase Ib cohorts with DCDT2980S administered at doses of 1.8 mg/kg (5 patients) and 2.4 mg/kg (11 patients) in combination with 375 mg/m^2 rituximab.

Enrollment into CLL dose escalation cohorts was closed on 31 May 2013. Refer to the DCDT2980S Investigator Brochure for details regarding clinical data in CLL patients.

b. Pharmacokinetics

The pharmacokinetics of DCDT2980S have been characterized in the Phase I Study DCT4862g. DCDT2980S was administered to patients with NHL at dose levels ranging from 0.1 to 3.2 mg/kg every 3 weeks (q3w). Three analytes were quantified: antibody-conjugated MMAE (acMMAE), total antibody, and free MMAE.

Preliminary PK analysis based on available data as of 22 June 2012 is summarized below.

The mean value of CL estimates of acMMAE and total antibody of each dose level for doses of ≥ 1.0 mg/kg ranged from 17.6 to 21.3 mL/day/kg and from 10.5 to 16.2 mL/day/kg, respectively. Similar CL estimates for doses ≥ 1.0 mg/kg suggested dose-proportional increase of acMMAE and total antibody exposure. CL estimates appeared to be slightly higher at doses < 1.0 mg/kg (0.1, 0.25, and 0.5 mg/kg), although data from these dose levels are limited. The CL of acMMAE was faster than that of total antibody at each dose level.

In patients with NHL, the mean value of the steady-state volume of distribution (V_{ss}) of acMMAE and total antibody of each dose level ranged from 69.2 to 130 mL/kg and from 97.4 to 154 mL/kg, respectively, across the dose levels tested, approximating human serum volume. V_{ss} values did not appear to change substantially with dose. The half-life for acMMAE and total antibody ranged from 2.9 to 7.0 days and from 4.4 to 13 days, respectively.

For acMMAE and total antibody, the time to maximum concentration occurred immediately after infusion. For free MMAE, the time to maximum concentration was approximately 2 to 3 days after infusion. Maximum plasma and serum concentration (C_{max}) and area under the concentration-time curve from Time 0 to infinity (AUC_{inf}) of free MMAE appeared to increase with dose across the dose levels tested. A half-life of 3-4 days for free MMAE was observed, which is relatively long and similar to that of its parent conjugate, suggesting formation rate–limited kinetics of free MMAE. No accumulation of free MMAE is expected for the q3w regimen. The C_{max} values of free MMAE in NHL patients were at least 100-fold lower than acMMAE concentrations at each dose level, suggesting a slow release of free MMAE from acMMAE and potentially fast elimination once it is formed.

Preliminary comparisons of pharmacokinetics between patients with NHL and CLL (for which patients are enrolled into separate dose-escalation cohorts) treated with identical doses of DCDT2980S provide some insight into the factors that affect pharmacokinetics. Both acMMAE and total antibody were cleared faster in CLL patients than in NHL patients. This observation is likely to be related to the high number of circulating B cells generally observed in CLL patients, which may result in significant target-mediated CL of DCDT2980S. The free MMAE exposure in CLL patients was relatively low compared to that of its parent conjugate.

The exposure parameters (C_{max} and AUC_{inf}) of total antibody, acMMAE, and free MMAE were similar between DCDT2980S and DCDT2980S + rituximab at doses of 1.8 and 2.4 mg/kg, based on preliminary data. This observation suggests that when given in combination, rituximab does not impact the pharmacokinetics of DCDT2980S; the effect of DCDT2980S on rituximab pharmacokinetics will be assessed.

All observations will be verified with additional data from the ongoing Phase I study as well as this study.

Refer to the DCDT2980S Investigator Brochure for complete and updated details.

c. Safety

Dose Limiting Toxicity

Study DCT4862g utilizes a standard 3+3 dose-escalation cohort enrollment scheme. Patients enrolled into each dose-escalation cohort in Study DCT4862g have been observed for dose-limiting toxicities (DLT) for a minimum of 21 days after their first dose of DCDT2980S. Any patient who did not complete the DLT observation period for any reason other than a DLT was replaced.

Separate dose-escalation cohorts enrolled patients with B-cell NHL and CLL. For the NHL dose escalation, DLTs of Grade 4 neutropenia occurred in 1 patient out of 3 DLT-evaluable patients in the 3.2 mg/kg single-agent cohort and 1 patient out of 11 DLT-evaluable patients in the 2.4 mg/kg + rituximab cohort. Consequently, DCDT2980S at 2.4 mg/kg was determined to be the recommended Phase II dose (RP2D) as both monotherapy and in combination with rituximab.

For the CLL dose-escalation cohorts, one DLT was reported to date. This Grade 5 event of febrile neutropenia resulted in the patient's death. Whereas the contribution of the study drug to the neutropenia could not be completely ruled out, other factors, including bone marrow involvement of disease that resulted in baseline anemia, thrombocytopenia and neutropenia, and clinical evidence of disease progression may have also played a contributory role.

Single-Agent DCDT2980S and DCDT2980S Combined with Rituximab in NHL

Forty-nine patients received single-agent DCDT2980S at a starting dose of $\geq$ 1.8 mg/kg (7 at 1.8 mg/kg, 42 at 2.4 mg/kg); 16 patients received DCDT2980S at a starting dose of $\geq$ 1.8 mg/kg in combination with rituximab (5 at 1.8 mg/kg, 11 at 2.4 mg/kg). Overall the safety profile of DCDT2980S combined with rituximab did not differ from that of single-agent DCDT2980S.

Treatment-emergent hematologic and commonly reported nonhematologic adverse events for all grades in patients treated with single-agent DCDT2980S and DCDT2980S plus rituximab included neutropenia (29%), febrile neutropenia (3%), infection (system organ class; 43%), anemia (25%), thrombocytopenia (12%), peripheral neuropathy

(28%), diarrhea (40%), pyrexia (14%), nausea (34%), and fatigue (55%). Treatment-emergent Grade ≥ 3 adverse events included neutropenia (25%), febrile neutropenia (3%), infection (system organ class; 11%), anemia (5%), peripheral neuropathy (3%), diarrhea (5%), pyrexia (2%), and fatigue (3%). Serious adverse events assessed by the treating investigator to be related to DCDT2980S were reported in 21% of patients. Dose discontinuations for adverse events were reported in 20% of patients.

Refer to the DCDT2980S Investigator's Brochure for complete and updated details related to safety.

d. Efficacy in Non-Hodgkin's Lymphoma

Investigator-based objective responses were observed in 17 of 43 (40%) patients treated with single-agent DCDT2980S and 5 of 15 (33%) patients treated with DCDT2980S combined with rituximab. Among patients with relapsed or refractory DLBCL, 11 of 28 (39%) objective responses (5 complete responses [CR] and 6 partial responses [PR]) were observed with single-agent DCDT2980S and 3 of 7 (43%; 2 CR, 1 PR) with DCDT2980S combined with rituximab. Among patients with relapsed or refractory indolent NHL (iNHL), 6 of 13 (46%) objective responses (2 CR, 4 PR) were observed with single-agent DCDT2980S and 1 of 4 (PR) with DCDT2980S combined with rituximab.

Refer to the DCDT2980S Investigator Brochure for complete and updated details related to anti-tumor activity.

1.2.2 DCDS4501A

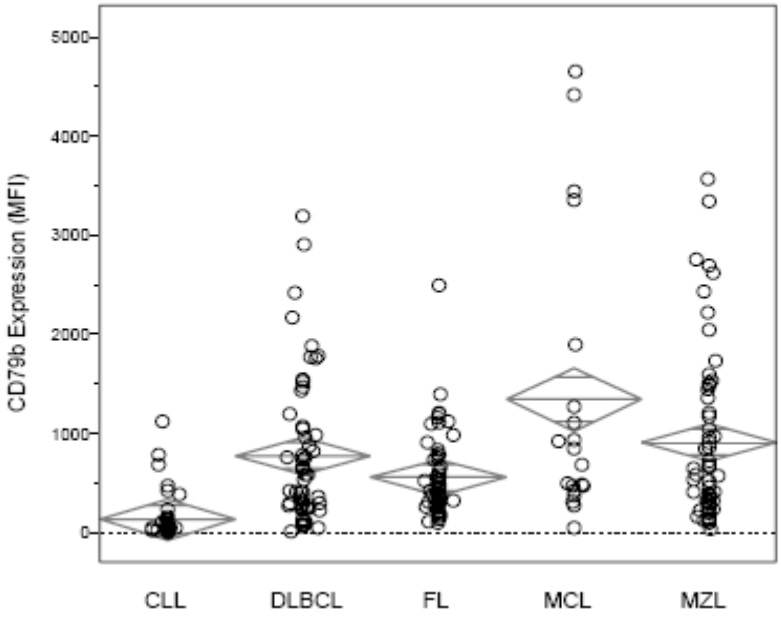
1.2.2.1 Background and Preclinical Data

CD79b is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of B cell–derived malignancies, including nearly all NHL and CLL samples tested (see Figure 2) (Dornan et al. 2009). Antibodies bound to CD79b are rapidly internalized, making CD79b ideally suited for targeted delivery of cytotoxic agents (Polson et al. 2007, 2009).

Similar to DCDT2980S, DCDS4501A is an ADC that contains a humanized immunoglobulin-G1 (IgG1) anti–human CD79b MAb (MCDS4409A) and MMAE linked through MC-VC-PABC.

Comprehensive pharmacologic, PK, PD, and toxicological evaluations were undertaken to support the entry of DCDS4501A into clinical trials. Because DCDS4501A specifically recognizes CD79b on B cells of human but not on those of cynomolgus monkey, rat, or mouse, a surrogate ADC (DCDS5017A) that binds to cynomolgus monkey CD79b was generated to assess the antigen-dependent pharmacological, toxicological, and PK/PD activities in cynomolgus monkeys. The structure, binding epitope, and binding affinity of the surrogate ADC are similar to those of DCDS4501A.

Figure 2 CD79b Expression Levels on B-Cell Tumor Cells



CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MFI = mean fluorescence intensity; MZL = marginal zone lymphoma.

CD79b expression levels (MFI) on B-cell tumor cells were assessed by flow cytometry in patients diagnosed with the following B-cell lymphomas: CLL (n = 49), DLBCL (n = 59), FL (n = 58), MCL (n = 20), and MZL (n = 60).

DCDS4501A bound human CD79b with high affinity ($K_d = 1.83 \pm 0.26$ nM); the surrogate ADC also showed similar high binding affinity to cynomolgus monkey CD79b. DCDS4501A displayed potent and selective inhibition of tumor cell proliferation in vitro ($IC_{50} = 0.071$ nM ± 0.01 nM) in cell viability assays. Moderate ADCC but no CDC activity was observed with the unconjugated clinical candidate antibody MCDS4409A. Both clinical and surrogate unconjugated antibodies showed no appreciable cytokine release when evaluated in in vitro cytokine release assays with PBMCs. Moderate elevations in interleukin (IL)-1α and interferon-inducible protein (IP)-10 were observed only with the unconjugated clinical antibody, however the clinical significance of these observations are not known because IL-1α and IP-10 are not produced by B cells, are not involved in B-cell signaling through CD79b, and are not associated with cytokine-release syndromes in vivo.

Single intravenous (IV) doses of DCDS4501A resulted in inhibition of tumor growth in murine xenograft models of lymphoma. Tumor regression was observed at doses ranging from 0.5 to 3 mg/kg. In contrast, MCDS4409A showed no activity. DCDS4501A administered at 5 mg/kg demonstrated better anti-tumor activity compared to a current standard-of-care regimen (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) in xenograft models of NHL. PD studies demonstrated that doses of the surrogate ADC ranging from 0.3 to 5 mg/kg resulted in a decrease of

peripheral blood B cells in cynomolgus monkeys. A preferential decrease of proliferating B cells ($CD20^+$ $Ki67^+$) compared to the resting B cells ($CD20^+$ $Ki67^-$)) by the surrogate ADC was demonstrated in cynomolgus monkeys, in line with the expected mechanism of action of an anti-mitotic agent, MMAE.

Due to B cell–mediated CL, non-linear pharmacokinetics were observed with the surrogate ADC in cynomolgus monkeys following single IV doses of 0.3–3 mg/kg or four doses of 3 and 5 mg/kg given q3w. The total antibody exposure after the fourth dose increased approximately 1.2- to 1.5-fold compared to the first dose. As expected, the toxicokinetic profile of the clinical ADC in rats and cynomolgus monkeys was linear in the tested dose range. Consistent with the half-life of the clinical ADC, minimal accumulation was observed following weekly dosing in rats and no accumulation was observed following q3w dosing in cynomolgus monkeys. The free MMAE concentrations in plasma following administration of the clinical or surrogate ADCs were generally low and overall did not exceed 2 ng/mL, regardless of dose. The overall incidence of anti-therapeutic antibodies (ATAs) was 20%–67% following administration of the clinical or surrogate ADCs in cynomolgus monkeys; however, the ATAs did not appear to impact the toxicokinetic/PK parameter estimates.

In repeat-dose toxicity studies in rats and cynomolgus monkeys, DCDS4501A and the surrogate ADC were well tolerated in monkeys up to doses of 5 mg/kg and 3 mg/kg respectively, with 3 mg/kg considered the HNSTD. In rats, DCDS4501A was well tolerated up to 6 mg/kg ($STD_{10} = 10$ mg/kg). The predominant antigen-independent findings associated with DCDS4501A or surrogate ADC exposure were reversible bone marrow toxicity and associated peripheral blood cell effects in both monkeys and rats. Administration of the surrogate ADC to monkeys also resulted in expected antigen-dependent reversible decreases in peripheral blood B cells and the disappearance of B-cell germinal centers in splenic lymphoid follicles at doses ≥ 3 mg/kg. Additional findings observed in rats but not in monkeys included thymic lymphoid depletion at ≥ 6 mg/kg, minimal to mild liver toxicities (at ≥ 6 mg/kg), lung toxicities at 10 mg/kg in male animals only, and a slight increase in apoptosis and mitoses in multiple tissues, including skin and adnexa. Hepatobiliary toxicity consisted of transient dose-dependent liver enzyme elevations accompanied by minimal to slight dose-dependent increases in mitotic figures/apoptosis in hepatocytes, sinusoidal cells, and bile duct epithelium as well as minimal to slight dose-dependent random focal hepatic necrosis. Pulmonary toxicity was characterized by minimal to slight dose-dependent alveolar macrophage infiltration, sometimes accompanied by minimal to slight type II pneumocyte hyperplasia/hypertrophy. These findings were consistent with the expected pharmacologic effect of MMAE on inducing mitotic arrest due to inhibition of tubulin polymerization. Except for two individual instances (one female given 10 mg/kg in the liver and one male given 10 mg/kg in the lung), these findings were completely reversible after a 6-week recovery period. Non-reversible male reproductive

toxicity, characterized by degeneration of testicular seminiferous tubules, was observed in rats at all doses.

Complete details of preclinical studies of DCDS4501A can be found in the DCDS4501A Investigator's Brochure.

1.2.2.2 DCDS4501A Clinical Data

a. Patient Enrollment

Both DCDS4501A monotherapy and combination therapy with rituximab are being studied in a Phase I study (Study DCS4968g) of patients with relapsed or refractory B-cell malignancies expected to express CD79b, including indolent NHL, DLBCL, MCL, and CLL.

All data presented herein is based on a data entry cutoff of 28 February 2013, with clinical data available from 60 patients with NHL (excluding patients with CLL) enrolled in dose-escalation and expansion cohorts. These include 51 patients who were treated with single-agent DCDS4501A ranging from 0.1 to 2.4 mg/kg administered intravenously every 21 days and 9 patients who were enrolled into a single Phase Ib cohort with DCDS4501A administered at a dose of 2.4 mg/kg in combination with 375 mg/m^2 rituximab.

In the CLL dose-escalation cohorts, two DLTs were reported at the single-agent dose of 1.8 mg/kg. Enrollment into the CLL cohorts was stopped on 7 January 2013. Refer to the DCDS4501A Investigator Brochure for details regarding clinical data in CLL patients.

b. Pharmacokinetics

The pharmacokinetics of DCDS4501A were characterized in the Phase I Study DCDS4501A. DCDS4501A was administered in patients with NHL at escalating doses of 0.1 to 2.4 mg/kg q3w as monotherapy and following administration of rituximab in the Phase Ib cohort. Three analytes were quantified: acMMAE, total antibody, and free MMAE.

Preliminary PK analysis based on available data as of 22 June 2012 is summarized below. The CL estimates of acMMAE and total antibody of each dose level is in the range of 14.9–21.2 mL/day/kg and 7.12–27.9 mL/day/kg, respectively. CL estimates were similar across doses of 0.1–2.4 mg/kg tested, suggesting dose-proportional increase of acMMAE and total antibody exposure. The CL of acMMAE was faster than that of total antibody at each dose level.

The mean value of V_{ss} of acMMAE and total antibody of each dose level ranged from 61 to 80.8 mL/kg and from 59.4 to 114.3 mL/kg, respectively, across the dose levels tested, which approximated human serum volume. V_{ss} values did not appear to change substantially with dose. The half-lives for acMMAE and total antibody are from 2.4 to 5.5 days and 2.9 to 7 days, respectively.

In a single-agent dose-escalation study, for acMMAE and total antibody, the time to maximum concentration occurred immediately after infusion. For free MMAE, the time to maximum concentration was approximately 2 to 3 days after infusion. C_{max} and AUC_{inf} of free MMAE appear increased with dose across the dose levels. A half-life of 3–4 days for free MMAE was observed, which is relatively long and similar to acMMAE and suggests formation rate–limited kinetics for free MMAE. No accumulation of free MMAE is expected for the q3w regimen. The C_{max} values of free MMAE in NHL patients were at least 100-fold lower compared with acMMAE concentrations at each dose level, suggesting a slow release of free MMAE from acMMAE and potentially fast elimination once it is formed.

Preliminary comparisons of pharmacokinetics between patients with NHL and CLL (for which patients are enrolled into separate dose-escalation cohorts) treated with identical doses of DCDS4501A provide some insight into the factors that affect pharmacokinetics. Both acMMAE and total antibody were cleared faster in CLL patients than in NHL patients. This observation is likely to be related to the high number of circulating B cells generally observed in CLL patients, which may result in significant target-mediated CL of DCDS4501A. The free MMAE exposure in CLL patients was relatively low compared with that of its parent conjugate.

To date, PK data for patients treated with DCDS4501A in combination with rituximab is limited. Consequently, full comparison with single-agent DCDS4501A pharmacokinetics is not possible. On the basis of very limited data from 3 patients, total antibody pharmacokinetics was comparable between 2.4 mg/kg of DCDS4501A administered as a single agent and following rituximab administration, suggesting that when given in combination, rituximab does not affect the pharmacokinetics of DCDS4501A; the effect of DCDS4501A on rituximab pharmacokinetics will be assessed.

All observations will be verified with additional data from the ongoing Phase I study as well as this study.

Refer to the DCDS4501A Investigator Brochure for complete and updated details.

c. Safety

Dose-Limiting Toxicities

Study DCS4968g utilizes a standard 3 + 3 dose escalation cohort enrollment scheme. Patients enrolled into each dose-escalation cohort in Study DCS4968g have been observed for DLTs for a minimum of 21 days after their first dose of DCDS4501A. Any patient who did not complete the DLT observation period for any reason other than a DLT was replaced.

DLT of Grade 4 neutropenia occurred in 1 patient out of 10 DLT-evaluable patients in the 2.4 mg/kg single-agent cohort and 1 patient out of 9 DLT-evaluable patients in the 2.4 mg/kg + rituximab cohort. Doses of DCDS4501A greater than 2.4 mg/kg as

monotherapy or in combination with rituximab were not assessed. Consequently, DCDS4501A at 2.4 mg/kg was therefore determined to be the RP2D as both monotherapy and in combination with rituximab. Patients are currently being enrolled in monotherapy expansion cohorts for various types of NHL in order to collect and further characterize both single-agent and combination safety data.

In the CLL dose-escalation cohorts, two DLTs were reported at the single-agent dose of 1.8 mg/kg. One patient had a Grade 4 neutropenia, and 1 patient had a Grade 4 invasive fungal infection.

Single-Agent DCDS4501A and DCDS4501A Combined with Rituximab

Fifty-one patients received single-agent DCDS4501A at a starting dose of ≥ 1.8 mg/kg (6 at 1.8 mg/kg, 45 at 2.4 mg/kg); an additional 9 patients received DCDS4501A at a dose of 2.4 mg/kg in combination with rituximab. Overall, the safety profile of DCDS4501A combined with rituximab did not differ from that of single-agent DCDS4501A.

Treatment-emergent hematologic and commonly reported non-hematologic adverse events of all grades in patients treated with single-agent DCDS4501A and DCDS4501A plus rituximab included neutropenia (50%), febrile neutropenia (5%), infection (system organ class; 35%), anemia (13%), thrombocytopenia (18%), peripheral neuropathy (32%), diarrhea (43%), pyrexia (37%), nausea (35%), and fatigue (18%). Treatment-emergent Grade ≥ 3 adverse events included neutropenia (43%), febrile neutropenia (5%), infection (system organ class; 10%), anemia (8%), peripheral neuropathy (7%), diarrhea (3%), pyrexia (2%), and fatigue (5%). Serious adverse events assessed by the treating investigator to be related to DCDS4501A were reported in 20% of patients. Dose discontinuations for adverse events were reported in 33% of patients.

Refer to the DCDS4501A Investigator's Brochure for complete and updated details related to safety.

d. Efficacy

Investigator-based objective responses were observed in 28 of 49 (57%) patients treated with single-agent DCDS4501A and 7 of 9 patients (78%) treated with DCDS4501A combined with rituximab. Among patients with relapsed or refractory DLBCL, objective responses were observed in 16 of 30 (53%; 4 CR, 12 PR) patients treated with DCDS4501A; 1 patient with DLBCL was treated with DCDS4501A combined with rituximab and achieved a PR. Among patients with relapsed or refractory iNHL, objective responses were observed in 7 of 14 (50%; 2 CR, 5 PR) patients treated with single-agent DCDS4501A and 5 of 5 (100%; 2 CR, 3 PR) patients treated with DCDS4501A plus rituximab.

Refer to the DCDS4501A Investigator Brochure for complete and updated details regarding anti-tumor activity.

1.2.3 Rituximab

Rituximab has been shown to be an effective treatment for CD20-positive B-cell malignancies and is commonly used both as a single agent and in combination with cytotoxic chemotherapy. Rituximab binds to CD20, a hydrophobic, transmembrane protein that is present on pre–B cells and mature B cells and in ≥ 90% of B-cell NHLs. It exerts its cytotoxic effects via complement-mediated B-cell lysis, ADCC, and induction of apoptosis (Cartron et al. 2004).

In the United States, rituximab has been approved by the U.S. Food and Drug Administration (FDA) for the following indications in NHL: as a single agent for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL; for the treatment of relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL, including initial treatment weekly for eight doses and re-treatment (weekly for four doses) in patients who responded to an initial course of rituximab; for the treatment of low-grade, CD20-positive B-cell NHL, in combination with cyclophosphamide, vincristine, and prednisone (CVP) induction chemotherapy in previously untreated patients with follicular, CD20-positive NHL; as treatment in previously untreated patients with low-grade, CD20-positive NHL who achieve an objective response or stable disease (SD) following CVP induction; and as maintenance therapy for previously untreated follicular CD20-positive B-cell NHL after achieving a response to a regimen including chemotherapy and rituximab.

In the European Union, rituximab (MabThera®) is approved for the treatment of the following indications in NHL: treatment of patients with Stage III–IV follicular NHL who are chemotherapy-resistant or in their second or subsequent relapse after chemotherapy; treatment of patients with CD20-positive DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy; as front-line therapy in Stage III–IV follicular NHL in combination with CVP chemotherapy; as maintenance therapy in patients with relapsed or refractory, follicular NHL responding to induction treatment with CHOP or R-CHOP; and as maintenance treatment for patients with FL who have responded to initial treatment with rituximab plus chemotherapy.

Rituximab has also been approved for the treatment of CLL. The European Medicines Agency (EMA) granted an approval for the use of rituximab in combination with chemotherapy for previously untreated CLL. The FDA approved the use of rituximab in combination with fludarabine and cyclophosphamide for patients with previously untreated and previously treated CD20-positive CLL.

Refer to the Rituximab Product Insert/Summary of Product Characteristics for complete details regarding clinical data related to approved indications. For rituximab safety information, refer to local rituximab prescribing information.

1.2.4 *Obinutuzumab*

1.2.4.1 *Obinutuzumab Mechanism of Action*

Obinutuzumab ([G], also known as RO5072759, GA101, Gazyva™, and Gazyvaro™) is a humanized type II and glycoengineered anti-CD20 MAb, derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics (Mössner et al. 2010; Golay et al. 2013):

- *High-affinity binding to CD20 antigen on B cells*
- *Type II binding mode to the CD20 antigen, leading to a more even distribution of bound antibody to the surface membrane of the B cell due to lack of CD20 translocation into lipid rafts after antibody binding and low complement activation and low complement-dependent cytotoxicity related to the recognition of the CD20 epitope*
- *Compared with the type I anti-CD20 antibodies rituximab or ofatumumab, increased ADCC and antibody-dependent cell-mediated phagocytosis (ADCP) related to an improved binding of obinutuzumab to the different allotypes of FcγRIIIa and FcγRIIIb expressed by natural killer (NK) cells , monocytes/macrophages and neutrophils*
- *Compared with rituximab, increased direct cell-death induction related to an elbow hinge amino exchange of the Fab region and type II binding of the CD20 epitope*

Obinutuzumab received FDA approval in November 2013 and EMA approval in July 2014 on the basis of the CLL-11 Study BO21004 for patients with relapsed Chronic Lymphocytic Leukemia. Obinutuzumab plus chlorambucil showed superiority over rituximab plus chlorambucil in all efficacy parameters such as overall response rate (ORR), complete remission rate (CRR), minimal residual disease (MRD), progression-free survival (PFS), event-free survival (EFS), and duration of response (DOR) (Goede et al. 2014).

Obinutuzumab is currently being explored in the treatment of lymphoid malignancies such as aggressive and indolent lymphomas (DLBCL, FL, and marginal zone lymphoma [MZL]). Preliminary data suggest possible increased anti-lymphoma efficacy over rituximab, a hypothesis that is currently being explored in several randomized trials, including a Phase III study of R-CHOP versus G-CHOP in first-line treatment of DLBCL, a Phase III study of R-chemotherapy (CHOP, CVP, or bendamustine) followed by rituximab maintenance compared with G-chemotherapy (CHOP, CVP, or bendamustine) followed by obinutuzumab maintenance in first-line treatment of FL and MZL, and a Phase III study of obinutuzumab combined with bendamustine compared with bendamustine in patients with rituximab-refractory indolent NHL.

1.2.4.2 *Obinutuzumab Nonclinical Toxicology*

The nonclinical toxicology of obinutuzumab has been evaluated in repeat-dose studies in cynomolgus monkeys given weekly IV (30-minute infusion) up to 26 weeks in duration and weekly SC injections for 4 weeks in duration. The high dose of 50 mg/kg in the 26-week study resulted in a steady-state area under the concentration-time curve from 0 to 24 hours (AUC_{0-24}) exposure of 341,000 μg•hr/mL, which is approximately 61-fold above that of the clinical exposure of 5584 μg•hr/mL.

Consistent with expected pharmacologic activity, obinutuzumab caused marked decreases in B cells, with corresponding lymphoid depletion in spleen and lymph nodes. Circulating CD40-positive mature B cells began to reverse after several months without treatment and maximally reversed to 7%–152% of baseline by 37 weeks. In addition, transient decreases in NK cells were observed; this finding is consistent with the pharmacologic effect of FcγRIIIa binding. Suspected opportunistic infections in as many as three unscheduled deaths were considered a possible secondary result of B-cell depletion.

Obinutuzumab was immunogenic in the cynomolgus monkey, which led to reduced systemic exposures in several animals and abrogation of the pharmacologic activity. Hypersensitivity reactions were noted that included systemic inflammation and infiltrates consistent with immune complex–mediated hypersensitivity reactions such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation and led to unscheduled termination in six animals.

Both the clinical IV formulation and the SC formulation of obinutuzumab were locally well tolerated across studies. No effects were present in male and female reproductive parameters included in the 26-week IV dose study. No obinutuzumab-related effects were observed on CNS, respiratory, or cardiovascular function.

In vitro assays using undiluted human whole blood measured significant increases in cytokine secretion caused by obinutuzumab, indicating that obinutuzumab has an increased propensity to trigger first infusion–related cytokine release in patients.

See the Obinutuzumab Investigator's Brochure for details on the nonclinical studies.

1.2.4.3 *Obinutuzumab Nonclinical Efficacy*

Obinutuzumab has in vivo efficacy superior to rituximab in various human lymphoma xenograft models. Both antibodies were tested in human SUDHL-4 cells (DLBCL model) injected subcutaneously in severe combined immunodeficient (SCID) beige mice. Rituximab administration was started when tumors were established and rapidly growing. Results showed that rituximab at 10 mg/kg inhibited tumor growth compared with rituximab at 1 mg/kg; however, increasing the rituximab dose to 30 mg/kg did not result in increased efficacy and rituximab was not able to achieve complete tumor regression. In contrast, obinutuzumab showed a dose-dependent increase in efficacy in

the range of 1–30 mg/kg. Results showed complete tumor regression in all animals and lasting tumor eradication in 9 of 10 animals at the highest dose of 30 mg/kg and in 1 of 10 animals at a dose of 10 mg/kg.

In another experiment, SUDHL4 xenografts in SCID mice were first treated with weekly rituximab 30 mg/kg. When the tumors became refractory to rituximab (Day 35), rituximab treatment was continued or changed to either weekly vehicle control or obinutuzumab 30 mg/kg. While tumors in control- and rituximab-treated mice continued to grow, obinutuzumab-treated mice showed control of tumor growth and lived until Day 61 when control or rituximab-treated mice had already been sacrificed.

Additional studies have also shown similar results, with obinutuzumab treatment controlling tumor growth, whereas vehicle- and rituximab-treated tumors were not controlled (Mössner et al. 2010).

See the Obinutuzumab Investigator's Brochure for details on the nonclinical studies.

1.2.4.4 *Obinutuzumab Clinical Experience*

As of July 2013, more than 1900 patients with CD20-positive malignant disease have been treated with obinutuzumab in clinical trials. Clinical data for obinutuzumab are available from six clinical trials, including three Phase I and Phase II studies of obinutuzumab monotherapy, a Phase Ib chemotherapy combination study in NHL (Study BO21000), and two Phase III studies (Study BO21004 in CLL and Study GAO4753g in NHL).

Infusion-related reactions (IRRs), mostly Grades 1 and 2, are the most common adverse events observed during therapy. IRRs have been associated predominantly with the first infusion, generally occurring early during the infusion, shortly after the infusion, or, in some cases, up to 24 hours after the completion of the infusion. In a few patients, concurrent signs of laboratory tumor lysis syndrome (TLS) were observed. The incidence and intensity of IRRs decreased strongly with subsequent infusions of obinutuzumab. On the basis of preliminary observations, extensive tumor burden, tumor factors, and host factors may be predisposing factors for the occurrence of IRRs. The frequency and severity of IRRs is also reduced in lymphomas compared with CLL.

Other frequently observed adverse events include infections and neutropenia. Grade 3–4 thrombocytopenia and neutropenia, including febrile neutropenia, have been reported with obinutuzumab, associated predominantly with treatment of CLL rather than NHL. Given its anticipated mode of action, which results in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections during and after treatment.

Data from Study BO20999 (obinutuzumab monotherapy) showed safety and efficacy of single-agent obinutuzumab in patients with relapsed indolent and aggressive lymphomas. Responses were seen at both lower (400 mg) and higher (1600/800 mg) doses, although responses increased at the higher dose, with 54% of patients with indolent lymphoma and 32% of patients with aggressive lymphomas showing PR or CR at the end of treatment (EOT) (Morschhauser et al. 2013; Salles et al. 2013).

Study BO21000 (Phase Ib) evaluated obinutuzumab in combination with chemotherapy: obinutuzumab with fludarabine and cyclophosphamide and obinutuzumab with CHOP (Radford et al. 2013). Both chemotherapy combinations were shown to be feasible in patients with previously untreated or relapsed or refractory FL, with response rates of >90% for both regimens. Safety was acceptable, with no new or unexpected adverse events observed. The most common adverse event was neutropenia.

Data from obinutuzumab in combination with chlorambucil in CLL (Phase III Study BO21004) showed increased efficacy of this combination over rituximab-chlorambucil, with a hazard ratio of 0.39 for PFS. IRRs were common (65% all grades, 20% Grade 3–4, no fatal IRRs) and neutropenia occurred at increased frequency with the combination therapy (33% Grade 3–5), but there was no increase in infections or treatment-related deaths (Goede et al. 2014).

See the Obinutuzumab Investigator's Brochure for additional details on the clinical studies.

1.2.4.5 *Obinutuzumab Pharmacokinetics and Pharmacodynamics*

A two-compartment model comprising a time-varying CL pathway and a linear CL pathway provides an adequate description of the pharmacokinetics of obinutuzumab following IV administration in Study BO20999 and Study BO21003. Following the infusion of obinutuzumab, the elimination appears to be characterized by a linear CL pathway that is dependent on time (i.e., starting at a typical value of 630 mL/day and then gradually decreasing to an asymptote of 60 mL/day at steady state). Tumor burden may potentially contribute significantly to the CL of obinutuzumab, especially at the beginning of treatment when CD20-positive tumor cells are most abundant. As tumor burden decreases, the CL reaches an asymptote, which is considered to be primarily a function of the proteolytic metabolic CL. Some patients with a high tumor burden may appear to clear the drug from the plasma faster than patients with a low tumor burden because obinutuzumab binds to the CD20-positive tumor cells and is effectively removed from the plasma. The CL of the drug will vary with time because repeated treatments with obinutuzumab will reduce the quantity of CD20-positive tumor cells. The number of times obinutuzumab is administered during the first cycle of treatment may be expected to reduce the number of CD20-positive tumor cells, thus minimizing the impact of the time-varying CL pathway on obinutuzumab exposure.

Treatment with obinutuzumab resulted in extensive B-cell depletion, with all patients showing a reduction in B-cell counts to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before and after infusion, but transient increases occurring during the administration of obinutuzumab have been observed in the levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-10, and interferon (IFN)-γ.

1.3 RATIONALE FOR DOING THIS STUDY

The goals of this study are to continue to assess the safety, tolerability, and biologic and clinical activity of the combinations of DCDT2980S and rituximab and DCDS4501A and rituximab in two specific NHL patient populations: patients with relapsed or refractory follicular NHL and patients with relapsed or refractory DLBCL. *An additional goal of this study is to assess the safety, tolerability, and potential biologic and clinical activity of DCDS4501A in combination with obinutuzumab, an anti-CD20 antibody, in the aforementioned NHL patient populations.* These patients continue to have an extremely poor prognosis with no curative options available. Consequently, new therapeutic options are needed.

DCDT2980S, DCDS4501A*,* rituximab, *and obinutuzumab* each target antigens specific to B-cell malignancies including follicular NHL and DLBCL (see Figures 1 and 2).

The randomized component of the Phase II study design permits an assessment of the clinical benefit provided by each of these molecules in combination with rituximab, which has established clinical activity in B-cell malignancies both as monotherapy and in combination with chemotherapy. Data from this study will help inform the feasibility of the combination regimens in earlier lines of therapy (e.g., as first-line therapy in newly diagnosed patients).

The non-randomized component of the study will further evaluate the safety and tolerability and clinical activity of DCDS4501A in combination with obinutuzumab in patients with relapsed or refractory follicular lymphoma or DLBCL and will also provide preliminary evidence as to which anti-CD20 agent, rituximab or obinutuzumab, in combination with DCDS4501A, provides a better benefit-risk profile in the target population being studied.

The feasibility of combining an ADC with rituximab has previously been tested clinically with the combination of another, different CD22-specific ADC, inotuzumab ozogamicin (CMC-544), with results suggesting that the addition of rituximab may have increased clinical activity without significant increase in toxicity over the ADC alone in patients with aggressive NHL (Luis et al. 2006; Nam et al. 2009; Nina et al. 2010). As noted in Sections 1.2.1 and 1.2.2, the combinations of DCDT2980S and rituximab, and DCDS4501A and rituximab have been shown to have acceptable safety in patients with relapsed or refractory NHL in the Phase I studies (Studies DCT4862g and DCS4968g).

Given the relatively poor prognosis of patients with relapsed or refractory hematologic malignancies that have failed standard therapies, the nonclinical toxicity profile associated with DCDT2980S and DCDS4501A treatment, and the clinical safety profile observed to date for both ADCs, the benefit-risk ratio of a clinical study of DCDT2980S and DCDS4501A, each combined with rituximab *or obinutuzumab*, is considered acceptable.

1.3.1 Rationale for Assessing ADC Dose of 1.8 mg/kg Combined with Rituximab in iNHL

On the basis of available Phase I data (see Sections 1.2.1 and 1.2.2), both DCDT2980S and DCDS4501A as single agents and combined with rituximab have shown early signs of clinical activity in heavily pretreated patients with relapsed or refractory NHL. However, early evidence in the Phase I studies indicate that duration of study treatment may be limited by tolerability to ADC. Specifically, for both ADCs, peripheral sensory neuropathy has been identified as a known risk (see Section 3.4.3.5). Notably, 4 of 7 and 5 of 11 discontinuations for adverse events in Studies DCT4862g and DCS4968g, respectively, were the result of peripheral neuropathy.

Because of the chronic course and incurability of iNHL, treatment paradigms are increasingly emphasizing tolerability to treatment in addition to efficacy. As both DCDT2980S and DCDS4501A have shown single-agent activity at the 1.8 mg/kg dose level (Advani et al. 2012; Palanca-Wessels et al. 2012), the purpose of enrolling additional cohorts of patients with FL is to determine whether lower doses of ADC in combination with standard doses of rituximab result in improved tolerability while maintaining efficacy in FL.

In contrast to iNHL, treatment paradigms in relapsed or refractory aggressive lymphomas such as DLBCL continue to place a premium on anti-tumor activity and higher tolerance for treatment-related toxicity, given that durations of disease control and survival are substantially shorter and that treatment options are extremely limited. Early Phase I data suggest lower rates of study treatment discontinuation for adverse events among patients with DLBCL compared with patients with iNHL. Taken together with anti-tumor activity observed to date, the benefit-risk profile of the currently tested ADC dose of 2.4 mg/kg is considered acceptable

1.3.2 *Rationale for Assessing DCDS4501A in Combination with Obinutuzumab in Relapsed or Refractory NHL*

The development of next-generation anti-CD20–directed therapy may further enhance the efficacy of current standard regimens for NHL. Obinutuzumab, also known as RO5072759, GA101, and Gazyva™/Gazyvaro™, a novel type II and glycoengineered anti-CD20 antibody, has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). Obinutuzumab is currently being compared with rituximab in two large Phase III studies in patients with newly diagnosed DLBCL (Study BO21005) and with previously untreated iNHL, including FL

(Study BO21223). Assuming these studies demonstrate greater clinical benefit with obinutuzumab- vs. rituximab-containing regimens, potentially altering the standard of care in NHL, it will be important to also assess the safety and efficacy of combining DCDS4501A with obinutuzumab-containing regimens.

The goals of the non-randomized portion of the Phase Ib study are to assess the safety, tolerability, and potential biologic and clinical activity of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in patients with relapsed or refractory follicular NHL or DLBCL. The RP2D, the Phase II dose-expansion portion of the study, will further evaluate the safety and tolerability and clinical activity of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in patients with relapsed or refractory follicular NHL or DLBCL.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objectives of this study are the following:

- To assess the safety and tolerability of the combination of DCDT2980S and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the safety and tolerability of the combination of DCDS4501A and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- *To assess the safety and tolerability of the combination of DCDS4501A and obinutuzumab when administered to patients with relapsed or refractory follicular NHL or DLBCL*
- To assess the anti-tumor activity of the combination of DCDT2980S and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- *To assess the anti-tumor activity of the combination of DCDS4501A and obinutuzumab in patients with relapsed or refractory follicular NHL and DLBCL*

2.2 SECONDARY OBJECTIVES

2.2.1 Safety Objectives

The secondary safety objectives of this study are the following:

- To assess the incidence of antibody formation to DCDT2980S, DCDS4501A*, and obinutuzumab as measured by the formation of ATAs*
- To compare the safety and tolerability of the combination of DCT2980S and rituximab and DCDS4501A and rituximab *or obinutuzumab*

2.2.2 Activity Objective

The secondary activity objective of the study is the following:

- To compare the anti-tumor activity of the combination of DCT2980S and rituximab and DCDS4501A and rituximab *or obinutuzumab*

2.2.3 Pharmacokinetic Objectives

The PK objectives of this study are the following:

- To characterize the pharmacokinetics of DCDT2980S and rituximab in patients with relapsed or refractory NHL when the two drugs are given in combination
- To characterize the pharmacokinetics of DCDS4501A and rituximab *or obinutuzumab* in patients with relapsed or refractory NHL when the two drugs are given in combination

2.3 EXPLORATORY OBJECTIVES

2.3.1 Biomarker Objectives

The objectives of this study related to assessment of biologic markers are the following:

- To make a preliminary assessment of biologic markers that might act as predictors of DCDT2980S + rituximab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL
- To make a preliminary assessment of biologic markers that might act as predictors of DCDS4501A + rituximab *or obinutuzumab* combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL

2.3.2 Patient-*Reported Outcomes Objective*

The objective of this study related to assessment of *patient-reported outcomes (PRO)* is the following:

- To assess patient-*reported* tolerability to study treatment and the impact of study treatment on patient *functioning* on the basis of PRO

2.3.3 Crossover Treatment Objective

The objective of this study related to assessment of crossover treatment is the following:

- To preliminarily assess the safety, tolerability, and anti-tumor activity of DCDT2980S and DCDS4501A, either as a single-agent or in combination with rituximab, as crossover treatment following disease progression on initial study treatment. (Note: This objective applies only to patients enrolled in Arms A and B [see Section 3.1].)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase *Ib/*II, multicenter, open-label study. *Up to approximately 252* patients with relapsed or refractory *FL and* DLBCL will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain

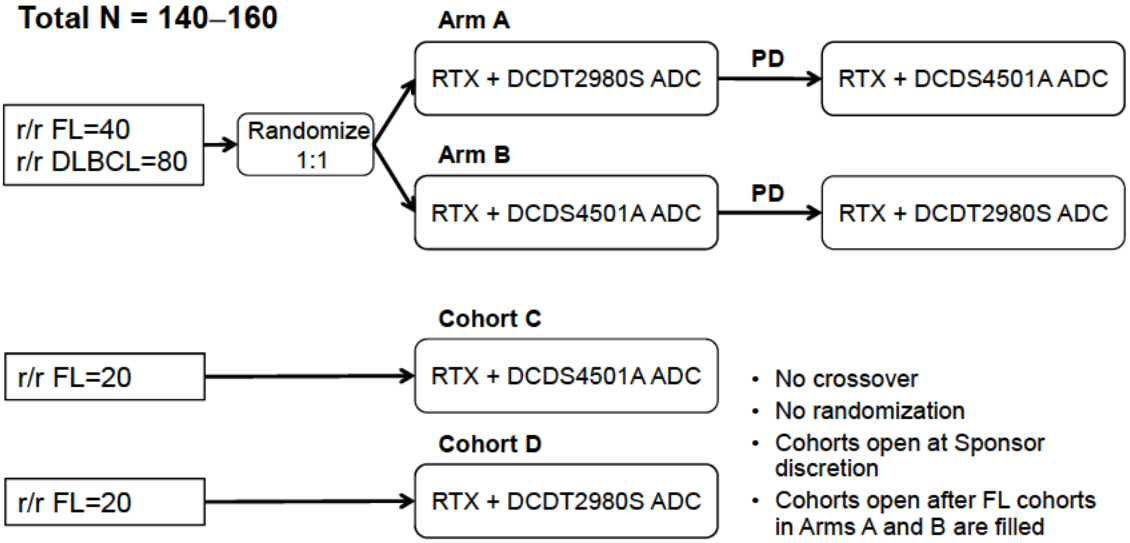
additional safety and/or efficacy data. *Arms A and B and Cohort C are no longer enrolling patients.*

For Obinutuzumab Cohorts:

Only investigational sites in the United States will enroll patients into Cohort E. Investigational sites in the United States and Canada will participate in Cohorts G and H).

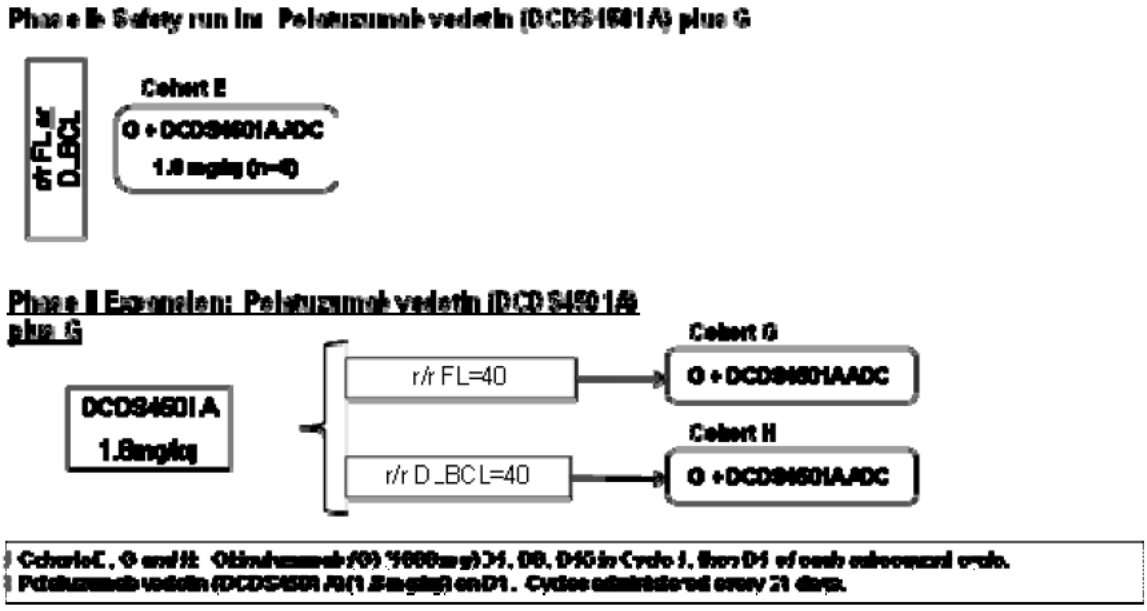
The study will be composed of a randomized portion and a non-randomized portion, as illustrated in Figure 3.

Figure 3*a* Study Schema *for Rituximab-Containing Arms/Cohorts*



Arms A and B: RTX (375 mg/m^2) + ADC (2.4 mg/kg) administered in every-21-day cycles.
Cohorts C and D: RTX (375 mg/m^2) + ADC (1.8 mg/kg) administered in every-21-day cycles.

Figure 3b Study Schema for Obinutuzumab-Containing Arms/Cohorts



ADC=antibody-drug conjugate; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; *G=GA101/obinutuzumab;* PD=progressive disease; r/r=relapsed or refractory; RTX=rituximab.

3.1.1 *Rituximab-Containing Regimens with DCDT2980S or DCDS4501A*

3.1.1.1 Randomized Portion of the Study (Arms A and B)

Following determination of eligibility, patients within each disease group will be randomized in a 1:1 ratio to receive one of two treatments:

- Arm A: Rituximab (375 mg/m^2) followed by DCDT2980S (2.4 mg/kg) every 21 days;
- Arm B: Rituximab (375 mg/m^2) followed by DCDS4501A (2.4 mg/kg) every 21 days

The first day of treatment constitutes Day 1 of each cycle. A typical cycle is 21 days in duration.

A dynamic hierarchical randomization scheme will be employed with respect to the following stratification factors:

- For patients with FL (see Section 3.1.4 for definitions)

  Rituximab refractory disease (no response or disease relapse $<$6 months from last rituximab treatment) versus rituximab relapsed disease (disease relapse after response $\geq$ 6 months from last rituximab treatment)

- For patients with DLBCL (see Section 3.1.5 for definitions)

  Second-line versus third-line (or beyond) therapy

  For second-line patients, disease relapse or no objective response (CR, unconfirmed CR [CRu], or PR) <12 months from the start of initial therapy versus disease relapse, after initial objective response (CR, unconfirmed response [CRu] or PR), $\geq$ 12 months from start of initial therapy

  For third-line patients, failure to achieve a CR or progression < 6 months from start of most recent therapy versus CR or progression ≥ 6 months from start of most recent therapy

No formal testing comparing the two treatment arms in the randomized portion of the study is planned.

3.1.1.2 Non-Randomized Portion of the Study *with Rituximab* (Cohorts C and D)

Only select investigator sites that have agreed to participate in the non-randomized portion of the study will enroll patients into these cohorts.

Patients with relapsed or refractory follicular NHL will be enrolled in Cohorts C and D to receive rituximab (375 mg/m^2) combined with DCDT2980S or DCDS4501A at a dose of 1.8 mg/kg. The first day of treatment constitutes Day 1 of each cycle. A typical cycle will be 21 days in duration.

The opening of either or both cohorts will be at the Sponsor's discretion and only after the enrollment of patients with FL into the randomized portion of the study is completed.

Patients will not be randomized to receive one treatment or the other. It is anticipated that Cohort C and D will be opened sequentially.

3.1.2 **All Patients** *on Rituximab-Containing Arms/Cohorts*

All patients *on rituximab-containing regimens*, regardless of assigned arm/cohort, will receive DCDT2980S or DCDS4501A and rituximab administered by IV infusion on a 21-day cycle. For the first two cycles, rituximab will be administered by IV infusion on Day 1 and DCDT2980S or DCDS4501A will be administered by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this instance, rituximab will be administered first, followed by DCDT2980S or DCDS4501A. In certain circumstances—for example, IRRs requiring interruption or slowing of infusion rate—rituximab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDT2980S or DCDS4501A may be administered on Day 2 following completion of the rituximab infusion or on Day 3 of the cycle.

Patients may receive treatments for up to 1 year (17 cycles on an every-21-day schedule) if not discontinued because of significant toxicity, disease progression, or withdrawal from study.

Patients will be evaluated for safety and efficacy according to the Schedules of Assessments outlined in Appendices A-1, A-2, and A-*4*. Initial response assessments in this study will be performed every 3 months from the initiation of therapy until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). Additional response assessments for patients who proceed to crossover treatment (see Section 3.1.6) will be performed as described in Appendix A-2; response assessments for patients who discontinue study treatment (both initially assigned treatment and crossover treatment) for reasons other than disease progression will be performed as described in Appendix A-*4*.

Responses to study treatment will be based on investigator assessments. In addition, tumor assessment data will be transmitted to an Independent Review Facility (IRF) for collection and possible independent review.

3.1.3 *Obinutuzumab-Containing Regimen with DCDS4501A (Cohorts E, G, and H)*

DCDS4501A at 1.8 mg/kg will be given in combination with obinutuzumab to patients with relapsed or refractory follicular NHL and DLBCL in two stages: (1) safety run-in and (2) expansion.

Study treatment will be given in 21-day cycles for both follicular NHL and DLBCL. Patients will be treated for up to a total of 8 cycles. For the first cycle, obinutuzumab

will be administered by IV infusion on Days 1, 8, and 15. DCDS4501A will be given on Day 2 for Cycle 1. In the absence of any infusion-related adverse events, obinutuzumab and DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the second cycle. If obinutuzumab and DCDS4501A are administered on the same day, the study drugs will be given sequentially. Obinutuzumab will be administered first, followed by DCDS4501A. In certain circumstances—for example, IRRs requiring interruption or slowing of infusion rate—obinutuzumab may be administered over 2 days (e.g., Day 1 and Day 2 of the cycle); in this case, DCDS4501A may be administered on Day 2 following completion of the obinutuzumab infusion.

3.1.3.1 *Obinutuzumab-Containing Regimen in Phase Ib: Safety Run-In (Cohort E)*

This portion of the study will consist of a safety run-in that will evaluate the safety of DCDS4501A at 1.8 mg/kg in combination with obinutuzumab in 6 patients (Cohort E). The safety run-in is described in detail in Section 3.4. In case an amendment to the protocol allows to study higher doses of DCDS4501A, the safety run-in for the 1.8 mg/kg may be shortened to 3 patients.

Obinutuzumab-Containing Regimens in Phase II: Expansion Stage (Cohorts G and H)

After the safety run-in has demonstrated that DCDS4501A at 1.8 mg/kg in combination with obinutuzumab is safe to administer, patients will be enrolled into two expansion cohorts based on histology of follicular NHL or DLBCL (Cohorts G and H, respectively). Forty patients will be enrolled into each expansion cohort. An additional cohort(s) may be added in the future.

3.1.4 **Follicular NHL** *Patients for Rituximab-Containing Arms/Cohorts*

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed as documented history of response (CR, CRu, or PR) of ≥6 months in duration from completion of all prior rituximab-containing regimens. A rituximab-containing regimen is defined as rituximab as a single agent during induction and/or maintenance or in combination with other agents during induction and/or maintenance.
- Refractory to any prior regimen containing rituximab, defined as no response to or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:

  Patients with progressive disease while receiving rituximab monotherapy, rituximab combined with chemotherapy, or rituximab maintenance therapy; patients must have received at least one full dose (375 mg/m^2) of rituximab.

Patients with no objective response (PR or CR) to a rituximab-containing regimen consisting of at least 4 weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Patients with disease relapse, after having achieved an objective response, within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Enrollment of patients with refractory disease as defined above may be limited to no greater than 60% of the total follicular NHL cohort, in order to avoid overrepresentation of the refractory disease population.

3.1.5 *Follicular NHL Patients for Obinutuzumab-Containing Cohorts*

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- *Relapsed to prior regimen(s) after having a documented history of response (CR, CRu, or PR) of ≥6 months in duration from completion of regimen(s)*
- *Refractory to any prior regimen, defined as no response to the prior therapy, or progression within 6 months of completion of the last dose of therapy*

3.1.6 **DLBCL** *Patients for Rituximab-Containing Arms/Cohorts*

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/stem cell transplant (SCT) will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) < 12 months from start of initial therapy (second-line refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response ≥ 12 months from start of initial therapy (second-line relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) < 6 months from start of prior therapy (third-line + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response ≥ 6 months from start of prior therapy (third-line + relapsed)

Enrollment into any of the above four categories may be limited to no greater than 40% of the DLBCL cohort—and to no more than 60% of the two refractory categories combined—in order to avoid overrepresentation of any specific subpopulation, refractory patients in particular.

3.1.7 *DLBCL Patients for Obinutuzumab-Containing Cohorts*

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high-dose therapy with autologous stem cell rescue/SCT will be enrolled into the study as defined by the following:

- *Second-line SCT-ineligible patients with progressive disease or no response (SD) <12 months from start of initial therapy (second-line refractory)*
- *Second-line SCT-ineligible patients with disease relapse after initial response ≥12 months from start of initial therapy (second-line relapsed)*
- *Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) <6 months from start of prior therapy (third-line +refractory)*
- *Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response ≥6 months from start of prior therapy (third-line + relapsed)*

3.1.8 Crossover Treatment (Randomized Patients *in Arms A and B* Only)

Patients randomized to Arm A or Arm B who develop progressive disease may be eligible to receive crossover treatment consisting of rituximab and the other ADC or the other ADC alone—for example, Arm B treatment for patients who have disease progression while receiving Arm A treatment, and vice versa—provided the following conditions are met:

- Patients must not have experienced a toxicity requiring the discontinuation of DCDT2980S/DCDS4501A treatment OR experienced toxicity during the last dose of study treatment that would preclude treatment with the crossover regimen.

  Patients who had modifications to dosing and/or schedule on the initial study treatment will be permitted to receive crossover treatment in the absence of toxicities on the modified dose and/or schedule. The dose and schedule of crossover treatment will be determined by the investigator and the Medical Monitor.

  Patients who had rituximab discontinued and continued on single-agent DCDT2980S/DCDS4501A treatment may receive crossover treatment of single-agent DCDS4501A/ DCDT2980S.
- Patients must have radiographically documented disease progression.
- Patients must meet all inclusion and exclusion criteria described in Sections 4.1.1 and 4.1.2, except for those related to prior rituximab treatment.
- Acceptable toxicity: All study drug–related adverse events from the initial study treatment must have decreased to Grade 1 or baseline grade on or before the first day of treatment on the crossover regimen. Exceptions may be allowed after a careful assessment and discussion of the benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.

- Administration of crossover treatment must be in the best interests of the patient as determined after a careful assessment and discussion of benefit-risk balance with the patient by the investigator and approval from the Medical Monitor.
- A tumor biopsy (see Section 4.5.1.9) will be required for patients with safely accessible site of disease, defined as requiring only local anesthesia and, in general, excluding the brain, lungs or any internal organs that may subject patients to significant risk.

  Patients for whom a safely accessible site of disease is not present may still receive crossover treatment without undergoing a biopsy. Eligibility to receive crossover treatment should be discussed with and approved by the Medical Monitor.

  A tumor biopsy of a safely accessible site of disease is optional for patients who are not eligible for study cross over.

Patients who are determined to be eligible for study cross over will be treated as follows:

- Assessments obtained at the initial study treatment discontinuation visit (see Section 4.5.4) may be used as screening assessments for crossover treatment. The following re-screening assessments must be repeated/obtained within 1 week prior to starting treatment on the crossover regimen, in order to re-establish baseline pretreatment clinical and disease status: targeted physical exam, Eastern Cooperative Oncology Group (ECOG) status, and hematology and serum chemistry laboratory tests.

  Re-screening tests for hepatitis B and C do not need to be performed unless there is clinical suspicion of hepatitis B and/or C positivity.

  A radiographic tumor assessment must also be performed, unless already done to document disease progression, within 6 weeks prior to starting crossover treatment.
- Crossover treatment will begin no later than 42 days after the last dose of the prior study treatment.

Patients will be treated with the crossover treatment until a second disease progression event relative to the tumor assessment, documenting progressive disease on the initial study treatment, clinical deterioration, and/or intolerance to the crossover treatment for up to a maximum of 1 year (17 cycles on an every-21-day schedule). Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in Appendices A-2. Response assessments for patients who discontinue study treatment for reasons other than disease progression will be performed as described in Appendix A-*4*.

Clinical data and exploratory data derived from tumor biopsies obtained prior to crossover treatment will be monitored on an ongoing basis. Genentech has the right to restrict or suspend enrollment into crossover treatment at any time. Reasons for this may include, but are not limited to, the following:

- The incidence or severity of adverse events during crossover treatment indicates a potential safety hazard to patients.
- Patient enrollment into crossover treatment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Patients who are enrolled into the non-randomized portion of the study (Cohorts C, D, *E, G, and H*) will not have the option to receive crossover treatment upon disease progression (see Section 3.2 for rationale).

3.2 RATIONALE FOR STUDY DESIGN

The primary rationale for the randomized non-comparative portion of the study is to assess clinical activity for the ADCs DCDT2980S and DCDS4501A in patients with relapsed or refractory NHL. The study design ensures that the patient populations under study are balanced with respect to critical variables such as prior therapy and ensures consistent clinical assessment of safety and efficacy. The collection and assessment of tumor tissue obtained prior to first study treatment and following progressive disease will provide further understanding of disease biology, possible mechanisms of resistance to the study treatment, and initial insights into tumor subtypes based on tumor biomarkers that are sensitive to study treatment. Finally, the inclusion of study treatment crossover (see Section 3.1.8) will address important questions regarding efficacy and tolerability of a second ADC-rituximab combination following disease progression on the initial ADC-rituximab combination.

The primary rationale for the non-randomized portion of the study *(Cohorts C and D)* is to assess the therapeutic index (i.e., the balance of efficacy and tolerability of DCDT2980S and DCDS4501A at a dose of 1.8 mg/kg in patients with relapsed or refractory follicular NHL). An informal comparison between patients with follicular NHL treated at the two doses of the ADC will help determine if tolerability is improved at the lower ADC dose without substantial compromise of efficacy.

The clinical feasibility of an ADC-rituximab combination regimen in patients with relapsed or refractory NHL has been previously studied. Results from studies of rituximab in combination with a different CD22-specific ADC, inotuzumab ozogamicin, demonstrated that when combined with rituximab, the ADC was able to be given at the single-agent MTD without the need for dose reduction of the ADC because of the lack of significant overlapping toxicity (Luis et al. 2006; Nam et al. 2009; Nina et al. 2010).

DCDT2980S and DCDS4501A are both being evaluated as single agents and in combination with rituximab in the ongoing Phase I studies Study DCT4862g and Study DCS4968g, respectively. Results from these trials have determined an MTD of 2.4 mg/kg for single-agent DCDT2980S and an RP2D of 2.4 mg/kg for single-agent

DCDS4501A in patients with mixed NHL. In addition, the RP2D of DCT2980S and DCDS4501 each in combination with rituximab (375 mg/m^2) on an every-21-day schedule was determined to be 2.4 mg/kg. Study GO27834 will continue to assess the cumulative safety and longer-term tolerability of ADC-rituximab combination therapy.

The primary rationale for the non-randomized Phase Ib/II obinutuzumab-containing cohorts (Cohorts E–H) is to assess safety and clinical activity for the combination of obinutuzumab and DCDS4501A in patients with relapsed/refractory NHL (Cohorts E, G, and H). Obinutuzumab (also known as RO5072759, GA101 and Gazyva™/Gazyvaro™), a novel type II and glycoengineered anti-CD20 antibody, has shown superiority over rituximab in a Phase III trial in first-line CLL (Goede et al. 2014). Obinutuzumab is currently being compared with rituximab in two large Phase III studies in patients with newly diagnosed DLBCL (Study BO21005) and previously untreated iNHL, including FL (Study BO21223). Assuming these studies demonstrate greater clinical benefit with obinutuzumab- vs. rituximab-containing regimens, potentially altering the standard of care in NHL, it will be important to also assess the safety and efficacy of combining DCDS4501A with obinutuzumab-containing regimens.

Study drug dosing will occur on Days 1 *or* 2 of each 21-day (or 28-day) cycle to allow for recovery from potential bone marrow toxicity.

3.2.1 Rationale for the PK Sample Schedule

PK data obtained in this study will be important in informing potential future trials with this combination. Given the likely changing effect of peripheral B-cell counts, tumor burden, and target antigen expression on target-mediated drug CL over multiple doses of DCDT2980S or DCDS4501A plus rituximab *or obinutuzumab* when the two drugs are given in combination, the drug levels of DCDT2980S or DCDS4501A-related analytes and rituximab *or obinutuzumab* will be assessed in this combination study.

In Studies DCT4862g and DCS4968g, single-agent DCDT2980S and DCDS4501A administered by IV infusion every 21 days were evaluated at doses ranging from 0.1 to 3.2 mg/kg for DCDT2980S and 0.1 mg/kg to 2.4 mg/kg for DCDS4501A in patients with NHL. Intensive PK sampling of all patients in the ongoing Phase I studies will provide sufficient data to allow complete profiling of the distribution and elimination phases for DCDT2980S and DCDS4501A and the investigation of potential correlations between various PK parameters and efficacy and/or toxicity. Consequently a reduced PK sampling scheme of DCDT2980S and DCDS4501A will be used in this study.

The PK data collected in this study will allow further characterization of the PK properties of DCDT2980S and DCDS4501A. In addition, the DCDT2980S and DCDS4501A concentration results from this study will be compared with available data from the single-agent clinical studies to evaluate whether concurrent administration of rituximab affects the exposure of DCDT2980S and/or DCDS4501A.

Rituximab serum concentration measurements from this study will be compared with PK data from historical rituximab clinical studies to evaluate whether the combination with DCDT2980S and/or DCDS4501A affects the pharmacokinetics of rituximab.

Limited sampling of serum concentrations of obinutuzumab will be assessed and compared with historical data to evaluate potential PK interactions with DCDS4501A.

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety and tolerability of the combination of DCDT2980S and rituximab and DCDS4501A and rituximab *or obinutuzumab* will be assessed using the following safety outcome measures:

- Incidence, nature, and severity of adverse events
- Incidence of anti-DCDT2980S*,* anti-DCDS4501A*, or anti-obinutuzumab* antibodies
- Changes in vital signs
- Changes in laboratory values

3.3.2 Pharmacokinetic/Pharmacodynamic Outcome Measures

The following PK parameters will be derived from the serum concentration–time profiles of total antibody (the sum of conjugated and unconjugated antibody), including rituximab *or obinutuzumab*, and plasma concentration-time profiles of acMMAE and free MMAE following administration of DCDT2980S or DCDS4501A, when appropriate, as data allow:

- Total exposure (area under the concentration-time curve [AUC])
- Maximum plasma and serum concentration (C_{max})
- CL
- Terminal half-life ($t_{1/2}$)
- V_{ss}

Compartmental, non-compartmental, and/or population methods may be used. Other parameters, such as accumulation ratio and trough plasma and serum concentration (C_{min}), may also be calculated.

The following PD outcome measures will be assessed when appropriate, as data allow:

- Peripheral blood B-cell depletion and recovery. For each visit at which $CD19^+$ B-cell measurements are taken, B-cell data will be listed for each patient by dose level as follows:

  Absolute blood cell counts

  Percent change relative to the baseline blood counts

CD19^{+} B-cell recovery, defined as the timepoint when the values return to baseline levels or ≥ 50% of baseline levels

- *Assessment of the kinetics of circulating tumor DNA*

3.3.3 Activity Outcome Measures

The following activity outcome measures will be assessed:

- Objective response, defined as a PR or CR
- Duration of objective response, defined as the *duration of time from the* first occurrence of a documented objective response *to* time of relapse or death from any cause
- PFS, defined as the *duration from* randomization to the first occurrence of progression or death within 30 days of the last administration of study drug, whichever occurs first
- OS, defined as the *duration* from the date of randomization*/enrollment* to the date of death from any cause

Objective response and disease progression will be determined using standard criteria for NHL (Cheson et al. 2007, 2014; see Appendix C-1 and Appendix C-2).

3.3.4 Exploratory Outcome Measures

The exploratory outcome measures will include, but will not be limited to, the following:

- Confirmation and quantitation of CD22, CD79b, and CD20 expression levels in either archival or freshly obtained (when available) tumor specimens (tumor biopsies, bone marrow biopsies, peripheral blood) by immunohistochemistry/flow cytometry/quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)
- Additional assessments related to the understanding of the mechanism of action of DCDT2980S, DCDS4501A, rituximab, *and obinutuzumab*, *e.g., assessment of circulating tumor DNA(ctDNA) to monitor response*, mechanisms of resistance to DCDT2980S, DCDS4501A*,* rituximab, *and obinutuzumab*, and/or NHL pathogenesis may be included.
- *Treatment and disease symptom* assessments using the M.D. Anderson Symptom Inventory (MDASI)

3.4 SAFETY PLAN

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

Safety will be evaluated through the monitoring of the following:

- Serious adverse events that are attributed to protocol-mandated interventions from the time of signing of the Informed Consent Form until the first dose of study treatment on Cycle 1, Day 1

- All adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A*,* rituximab, *or obinutuzumab,* whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A*,* rituximab, *or obinutuzumab,* whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from the last dose of DCDT2980S, DCDS4501A*,* rituximab, *or obinutuzumab,* whichever is later, including doses that were administered as part of crossover treatment, and which are judged to be caused by DCDT2980S, DCDS4501A*,* rituximab, *or obinutuzumab*, regardless of time of onset
- Measurements of protocol-specified hematology and clinical chemistry laboratory values
- Measurements of protocol-specified vital signs
- Assessment of ECGs
- Assessment of physical findings on clinical physical examinations

Patients who have an ongoing study drug–related adverse event will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, it is determined that the study treatment or participation is not the cause of the adverse event, or the study is terminated.

See Section 5.2.3 for assessment of causality for adverse events.

3.4.1 *Safety Run-In Analysis*

As outlined in Figure 3b and Section 3.1.3.1, a safety run-in analysis (Cohort E) will be conducted by the Internal Monitoring Committee (IMC) to evaluate the combination of DCDS4501A at a dose of 1.8 mg/kg with obinutuzumab. This analysis will include data from the first 6 patients treated through Day 21 of Cycle 1. Three patients will initially be enrolled, and then an additional 3 patients will be enrolled after the first 3 patients have safely completed the first cycle. At the IMC's discretion, and at any point during enrollment of the safety run-in, a decision could be made that more than 6 patients are needed to evaluate safety. In this case, the protocol will be amended to allow for more than 6 patients in the safety run-in. In case the study is amended to test additional doses the safety run-in for 1.8 mg/kg may be shortened to three patients.

Safety summaries will be assessed at the safety run-in for SAEs; Grade 3-5 treatment-related AEs; all AEs; all Grade 3-5 AEs; and AEs leading to treatment discontinuation or dose modification/interruption.

- *During the 6-patient safety run-in, if any patient experiences a treatment-related death, then the obinutuzumab-containing portion of the study will be closed to further recruitment.*

- *During the 6-patient safety run-in:*

  If 2 or more of the first 3 patients enrolled experience Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment

  If 1 of the first 3 patients enrolled experiences Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then an additional 3 patients will be recruited. If 2 or more of these first 3 patients experience Grade 4 febrile neutropenia or serious (i.e., SAE) infection with Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment.

  If 2 or more of the first 6 patients to be enrolled experiences Grade 4 febrile neutropenia or serious (i.e., SAE) documented infection requiring IV antibiotics in the presence of Grade 3–4 neutropenia, then the obinutuzumab-containing portion of the study will be closed to further recruitment.

  Before the expansion portion of the study can begin (enrollment of Cohorts G and H), the following criteria must be met:

    Six patients must have competed enrollment in the safety run-in (Cohort E).

    Three patients must have completed at least 4 cycles of treatment.

3.4.2 Internal Monitoring Committee

This study will employ an Internal Monitoring Committee (IMC). The purpose of the IMC will be to make recommendations regarding study conduct on the basis of trial safety data to ensure patient safety while receiving study treatment.

The IMC will include a sponsor Medical Monitor not affiliated with the study, a Drug Safety Scientist, a biostatistician, and a statistical programmer. Representatives from other Sponsor functional areas may be included as additional ad hoc members. In addition to the ongoing assessment of the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities by the Investigator and the Medical Monitor, the IMC will review the aforementioned data at least twice during the study.

Throughout the course of the study, the IMC will meet, as needed, at the request of the Medical Monitor (e.g., on the basis of unexpected safety signals). The IMC may make recommendations regarding study conduct, including, but not limited to, performing additional safety analyses, amending the study protocol, holding patient enrollment to one or both treatment arms pending further safety evaluations, holding/discontinuing study treatment, or terminating the study.

Complete details of the IMC will be described in the IMC charter.

For Arms A and B: The first planned review will occur after approximately 10 patients are randomized and have at least 6 weeks follow-up, and the next formal review will occur when approximately 60 patients are randomized and have at least 6 weeks follow-up.

3.4.3 Risks Associated with DCDT2980S and DCDS4501A

The clinical safety profile of DCDT2980S and DCDS4501A based on clinical data obtained in the ongoing Phase I studies are summarized in Sections 1.2.1.2 and 1.2.2.2. Known and suspected risks, based on clinical data to date, are described below. Guidelines regarding the management of these risks through dose and schedule modifications are described in Sections 4.3.1.3 and 4.3.1.4.

Refer also to the Investigator Brochure for complete and updated details.

3.4.3.1 Infusion-Related Events

Some MAbs may be associated with the development of allergic or anaphylactic reactions, to either the active protein or excipients. True allergic or anaphylactic reactions are rare after the first dose of a product, as they require prior sensitization. Patients with true allergic or anaphylactic reactions should not receive further doses of the product.

MAbs may also be associated with reactions that are clinically indistinguishable from true allergic or anaphylactic reactions but are mediated through direct release of cytokines or other pro-inflammatory mediators. Such reactions are often termed IRRs. IRRs typically occur with the first infusion of a MAb product and are generally less frequent and/or less severe with subsequent infusions. They can often be managed by slowing the infusion rate and/or pre-treatment with various medications.

Allergic or anaphylactic reactions and IRRs typically begin during or within several hours of completing the infusion. The onset of symptoms may be rapid, and some reactions may be life threatening.

Patients should be monitored for these types of reactions during and after receiving DCDT2908S and DCDS4501A. DCDT2980S and DCDS4501A should be administered in an environment under close supervision of a physician and where full resuscitation facilities are immediately available. Specific guidelines for additional precautions to be taken during and following DCDT2980S and DCDS4501A administration are provided in Sections 4.3.1.5.

3.4.3.2 Tumor Lysis Syndrome

There is a potential risk of TLS if treatment with DCDT2980S or DCDS4501A results in the rapid destruction of a large number of tumor cells. If any evidence of this occurs

during the study, TLS prophylaxis measures will be instituted. Patients who are considered to have a high tumor burden (e.g., lymphocyte count $\geq 25 \times 10^9$/L) or bulky lymphadenopathy and who are considered to be at risk for TLS by the investigator will receive TLS prophylaxis (e.g., allopurinol $\geq$300 mg/day orally or a suitable alternative treatment according to institutional practice starting 12–24 hours prior to study treatment) and must be well hydrated prior to the initiation of study treatment at Cycle 1, Day 1. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion as deemed appropriate by the investigator.

3.4.3.3 Bone Marrow Toxicity/Neutropenia

Based on preclinical toxicity studies in rats and cynomolgus monkeys and clinical data from the ongoing Phase I Studies DCT4862g and DCS4968g, neutropenia has been identified as a known risk (adverse drug reaction) of both DCDT2908S and DCDS4501A. Neutropenia and neutropenia-associated events were reversible but in some cases resulted in protocol-mandated dose reductions and/or delays.

Adequate hematologic function should be confirmed before initiation of study treatment. Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. *Study treatment may be delayed or modified due to* hematologic toxicities, as described in Section 4.3.1.

The use of G-CSF for neutropenia is described in Section 4.3.1.6. Transfusion support for anemia and thrombocytopenia is also permitted at the discretion of the treating physician.

Febrile neutropenia is commonly associated with myelotoxicity, which is considered a class effect of MMAE because it is commonly reported with ADCETRIS®, other similar ADCs, and vincristine sulfate.

Clinical data show that among the most common SAEs reported in both DCS4968g and DCT4862g studies were febrile neutropenia and pyrexia.

3.4.3.4 Immunogenicity

As expected with any recombinant antibody, DCDT2980S*,* DCDS4501A*, and obinutuzumab* may elicit an immune response and patients may develop antibodies against DCDT2980S*,* DCDS4501A*, or obinutuzumab*. Patients will be closely monitored for any potential immune response to DCDT2980S*,* DCDS4501A*, and obinutuzumab*. Appropriate screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with DCDT2980S*,* DCDS4501A*, and obinutuzumab*. Considering the historically low immunogenicity rate of rituximab in NHL patients, ATAs against rituximab will not be monitored in this study.

3.4.3.5 Peripheral Neuropathy

On the basis of clinical data from the ongoing Phase I Studies DCT4862g and DCS4968g and data from brentuximab vedotin studies, an anti-CD30-vc-MMAE ADC (see Section 3.4.2), peripheral neuropathy *(sensory and motor)* has been identified as a known risk (adverse drug reaction) for both DCDT2980S and DCDS4501A.

Careful clinical evaluation of patients for neuropathy should be conducted prior to initiation of study drug. Patients should be monitored for signs of *peripheral* neuropathy or worsening neuropathy and appropriate action taken per protocol guidelines. Study treatment dose and schedule modifications for significant and prolonged neuropathic toxicity and dose-reduction are described in Section 4.3.1.7.

3.4.3.6 Reproductive Toxicity

Adverse effects on human reproduction and fertility are anticipated with the administration of DCDT2980S and DCDS4501A, given the mechanism of action of MMAE. Standard exclusion criteria will be used to ensure that patients of childbearing potential (male or female) are using adequate contraceptive methods.

3.4.3.7 Hyperglycemia

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other ADCs using the same vc-MMAE platform. *Several patients given both DCDT2980S and DCDS4501A had abnormal fasting blood sugar (FBS) at screening with elevations of glucose following steroid administration prior to rituximab dose.* Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of anti-hyperglycemic medications. *Emerging data suggest that hyperglycemia may occur more commonly in individuals with abnormal FBS values or known diabetes. This is also reported for ADCETRIS® (2013 SmPC and 2013 USPI).*

3.4.3.8 Hepatotoxicity

Elevations in transaminase and/or bilirubin levels requiring dose modifications *and treatment discontinuations* have been reported in the ongoing clinical studies.

3.4.3.9 *Commonly Reported Side Effects*

Other commonly reported side effects of both DCDT2980S or DCDS4501A in the Phase I clinical trials and within this study include fatigue, nausea, decreased appetite, vomiting, hair thinning or loss, joint pains, loss of appetite, diarrhea, muscle aches, constipation, increases in blood glucose, and headaches.

3.4.4 Risks Associated with ADCETRIS® (Brentuximab Vedotin)

An ADC using the same MMAE drug and linker as that used in DCDT2980S and DCDS4501A, but coupled to an antibody targeting the CD30 antigen (brentuximab vedotin, ADCETRIS®, Seattle Genetics), was recently approved by the FDA for use in the treatment of specific subsets of patients with relapsed Hodgkin lymphoma and systemic anaplastic large-cell lymphoma.

The most common adverse reactions observed in studies with brentuximab vedotin (occurring in at least 20% of patients) were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting.

Serious adverse reactions were reported in 31% of patients receiving ADCETRIS®. The most common occurring in >2% of patients included peripheral motor neuropathy, abdominal pain, septic shock, supraventricular arrhythmia, pain in extremity, and urinary tract infection. In addition, John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has been reported.

Because of the use of the same MMAE drug, it is possible that the adverse events observed with the use of brentuximab vedotin can also be observed with the use of DCDT2980S and DCDS4501A.

Refer to the current version of the ADCETRIS® Prescribing Information for full and updated details.

3.4.5 Risks Associated with Rituximab Therapy and Their Management

3.4.5.1 Infusion Reactions

In single-agent clinical trials of rituximab and in post-marketing surveillance studies, mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first rituximab infusion. Other frequent infusion reaction signs and symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30–120 minutes of beginning the first infusion, and they resolved with slowing or interruption of the rituximab infusion and with supportive care (diphenhydramine, acetaminophen/paracetamol, IV saline, meperidine, and vasopressors). The incidence of infusion reactions was highest during the first infusion and decreased with each subsequent infusion.

Rituximab has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with a time to onset of 30–120 minutes. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm and may require interruption of rituximab administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events (see Appendix D). Approximately 80% of fatal infusion reactions occurred in association with the first infusion of rituximab. Because of this, patients should receive premedication with acetaminophen/paracetamol, antihistamines, or corticosteroids, in accordance with standard clinical practice, prior to rituximab infusions.

3.4.5.2 Management of Severe Infusion Reactions

Administration of rituximab will occur in a setting with emergency equipment and staff who are trained to monitor for and respond to medical emergencies. The rituximab infusion should be interrupted for severe reactions on the basis of clinical judgment.

Medications and supportive care measures—including, but not limited to, epinephrine, antihistamines, glucocorticoids, IV fluids, vasopressors, oxygen, bronchodilators and acetaminophen/paracetamol—should be available for immediate use and instituted as medically indicated for use in the event of a reaction during administration.

In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during all rituximab infusions include those with preexisting cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events, and those with high numbers of circulating malignant cells ($\geq$25,000/μL) with or without evidence of high tumor burden.

3.4.5.3 Tumor Lysis Syndrome

Rapid reductions in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia have been reported within 12–24 hours after the first infusion of rituximab. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with rituximab. The risks of TLS appear to be greater in patients with high tumor burden. Patients deemed to be at high risk for TLS complications may, at the investigator's discretion, receive their initial dose of rituximab over 2 consecutive days (see Section 4.3.2.3). Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of TLS complications, rituximab has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

3.4.5.4 Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported for some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately 1 month after the last dose of rituximab. Patients with serologic findings consistent with chronic HBV (hepatitis B surface antigen [HBsAg] positivity) or hepatitis C virus (HCV) infection (HCV RNA or antibody positivity) are ineligible for this study. Patients who are not chronically infected with HBV but have serologic evidence of prior infection at baseline (IgG hepatitis B core antibody[anti-HBc] positive but HBV DNA negative) may be eligible (if believed to be in the patient's best interest by the investigator and Medical Monitor) and would be monitored closely for perturbations in liver function during the period of rituximab

treatment and every 2–4 weeks thereafter. Such patients would also be required to receive prophylactic anti-viral therapy with lamivudine for at least 6 months after completion of rituximab therapy (Yeo et al. 2009).

Additional serious viral infections, new, reactivated, or exacerbated (e.g., infections caused by cytomegalovirus, varicella zoster virus, herpes simplex virus, West Nile virus, parvovirus B19, JC virus, and HCV) have been reported with rituximab, mainly in patients who had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Particular attention should be given to patients who have had significant prior immunosuppressive treatment such as high-dose chemotherapy and stem cell transplant. JC virus infection resulting in PML and death has been observed in rituximab-treated patients with hematologic malignancies or with autoimmune diseases. Most cases of PML were diagnosed within 12 months of the patient's last infusion of rituximab. Physicians should consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. Physicians should discontinue rituximab (and DCDT2980S and/or DCDS4501A) and consider discontinuation or reduction of any immunosuppressive therapy in patients who develop PML.

3.4.5.5 Cardiovascular Events

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with preexisting cardiac conditions, including arrhythmias and angina, who have had recurrences of these events during rituximab therapy should be monitored throughout the infusion and the immediate post-infusion period.

3.4.5.6 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, were observed in patients receiving rituximab in combination with chemotherapy for DLBCL. In post-marketing reports, which include patients with low-grade or follicular NHL and patients with DLBCL, the mean time to onset of symptoms was 6 days (range, 1–77 days) in patients with documented gastrointestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

3.4.5.7 Immunization

The safety of immunization with live viral vaccines following rituximab therapy has not been studied. Patients who participate in this study may not receive either primary or booster vaccination with live virus vaccines for at least 6 months prior to initiation of rituximab or at any time during study treatment. Investigators should review the vaccination status of potential study patients being considered for this study and follow

the U.S. Centers for Disease Control and Prevention guidelines for adult vaccination with non-live vaccines intended to prevent infectious diseases prior to study therapy.

Refer to the Rituxan®/MabThera® (Rituximab) Package Insert/Summary of Product Characteristics (SmPC) for additional safety information.

3.4.6 *Risks Associated with Obinutuzumab Therapy*

No evidence available at the time of the approval of this protocol indicates that special warnings or precautions are appropriate other than those noted in the Obinutuzumab Investigator's Brochure and as described in the following sections.

3.4.6.1 *Infusion-Related Reactions and Hypersensitivity Reactions (including Anaphylaxis)*

The commonly experienced IRRs have been characterized by fever, chills, flushing, nausea, vomiting, hypotension, hypertension, fatigue, and other symptoms.

Respiratory infusion-related symptoms, such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema, have also been reported. These IRRs were mostly mild or moderate (NCI CTCAE v4.0, Grade 1 and 2 events), and <10% of the events were severe (Grade 3 events), occurring predominantly during the first hour of the infusion or shortly after the first infusion had finished. The events resolved with the slowing or interruption of the infusion and supportive care. The incidence and severity of IRRs decreased with subsequent infusions. Extensive tumor burden predominantly localized in the blood circulation (e.g., high peripheral lymphocyte count in patients with CLL) may be a predisposing factor for the development of IRRs.

IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions.

3.4.6.2 *Tumor Lysis Syndrome*

TLS has been reported with obinutuzumab administration. Patients with a high tumor burden, including patients with a lymphocyte count ≥25 ×10^9/L, particularly patients with B-cell CLL and MCL, are at increased risk for TLS and severe IRRs. All patients with peripheral blood lymphocyte counts of ≥25 ×10^9/L or bulky adenopathy must receive prophylaxis for TLS prior to the initiation of study treatment. This includes appropriate hydration, consisting of fluid intake of approximately 3 L/day, starting 1–2 days prior to the first dose of obinutuzumab, and administration of allopurinol (300 mg/day orally) or a suitable alternative (i.e., rasburicase) treatment, starting at least 72 hours prior to the first infusion of obinutuzumab (Cycle 1, Day 1). All patients should then be carefully monitored during the initial weeks of treatment. Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts ≥25 ×10^9/L) before the second and subsequent infusions of obinutuzumab should receive continuous TLS prophylaxis with allopurinol

or a suitable alternative (i.e., rasburicase) and adequate hydration until the risk is abated, as determined by the investigator.

3.4.6.3 *Neutropenia*

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. Use of G-CSF has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G-CSF is allowed for treatment of neutropenia in this study. Primary prophylaxis with G-CSF is recommended according to the American Society of Clinical Oncology (ASCO), European Organisation for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines, namely for patients who are ≥60 years old and/or with co-morbidities (Lyman et al. 2004).

3.4.6.4 *Thrombocytopenia*

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in patients treated with obinutuzumab. It seems that the first cycle is the greatest risk of hemorrhage in patients treated with obinutuzumab. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants), may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician.

3.4.6.5 *Infection*

On the basis of its anticipated mode of action, resulting in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Infections have been reported in patients receiving obinutuzumab. Therefore, obinutuzumab should not be administered to patients with active severe infections.

A "black-box" warning for obinutuzumab states that reactivation of hepatitis B as well as other serious viral infections (e.g., infections caused by cytomegalovirus, Varicella zoster virus, herpes simplex virus, JC virus, and HCV) that were new, reactivated, or exacerbated have been reported with the B cell–depleting antibody rituximab mainly in patients who had received the drug in combination with chemotherapy or as part of a hematopoietic SCT. The risk of such infections with obinutuzumab is unknown.

Particular attention should be given to patients who have previously received significant immunosuppressive treatment, such as high-dose chemotherapy and SCT.

A "black-box" warning for obinutuzumab states that JC viral infection (including fatal) that resulted in PML with destructive infection of oligodendrocytes of the CNS white matte have been reported in patients treated with anti-CD20 therapies, including rituximab and obinutuzumab.

The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as cortical (e.g., aphasia or visual-spatial disorientation) can occur.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA).

Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the diagnosis and management of PML.

3.5 MINIMIZATION OF BIAS

For the randomized, non-comparative, open-label *portion of the* study*, p*atients *were* randomly allocated to two treatment arms in a 1:1 ratio through use of an Interactive Voice and Web Response System (IXRS). A dynamic stratified randomization scheme *was* employed to ensure balance in the stratification factors as specified in Section 3.1. *This portion of the study (Arms A and B) is now closed to enrollment.*

3.6 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche group, will sponsor this study. A Contract Research Organization (CRO) will be utilized to perform project management, study management, and clinical monitoring. Genentech will conduct CRO oversight, approve patient eligibility, and perform dose escalation decision-making, medical monitoring, and statistical programming and analysis. An IMC (see Section 3.4) will provide an additional level of safety monitoring for the study.

Approximately 40 study centers in the United States, Canada, and Europe will participate in the study to enroll approximately *252* patients. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

Electronic data capture (EDC) will be utilized for this study. An IXRS will be used to assign patient numbers. A central laboratory will be used for sample management and storage until shipment to one of several specialty laboratories or Genentech for analysis. An IRF will be used for the collection and possible assessment of radiographic images from tumor assessments. Additional vendors for ECG collection and possible analysis and for PRO collection and data entry will be used.

3.7 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with the FDA regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws, as well as other applicable country laws.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria to be eligible for study entry:

- Signed Informed
- Consent Form(s)
- Age ≥ 18 years
- ECOG Performance Status of 0, 1, or 2
- Life expectancy of at least 12 weeks
- History of histologically documented relapsed or refractory Grades 1–3a FL or relapsed or refractory DLBCL
- Availability of an archival or freshly biopsied tumor tissue sample must be confirmed for study enrollment.
- Have a clinical indication for treatment as determined by the investigator
- Must have at least one bidimensionally measurable lesion (>1.5 cm in its largest dimension by computed tomography [CT] scan or MRI)
- Laboratory values (including patients with hepatic or renal involvement), as follows:

  AST and ALT $\leq 2.5 \times$ ULN

  Total bilirubin $\leq 1.5 \times$ ULN

  Platelet count $\geq 75{,}000/mm^3$ (unless thrombocytopenia clearly due to marrow involvement of NHL and/or disease-related immune thrombocytopenia)

  Absolute neutrophil count $\geq 1000/mm^3$ (without growth factor support, unless neutropenia clearly due to marrow involvement of NHL)

  Total hemoglobin ≥ 9 g/dL (without transfusion support >14 days prior to screening, unless anemia clearly due to marrow involvement of NHL)

  Serum creatinine ≤ 2.0 mg/dL or measured creatinine CL ≥ 50 mL/min

- For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one highly effective form of nonhormonal contraception or two effective forms of nonhormonal contraception, **including at least one method with a failure rate of < 1% per year**, through the course of study treatment and for *≥12 months* after the last dose of DCDT2980S*,* DCDS4501A*,* rituximab, *or obinutuzumab* (whichever is later) in women and at least 5 months after the last dose of DCDT2980S*,* DCDS4501A*,* rituximab, *or obinutuzumab* (whichever is later) in men

  A woman is considered <u>not</u> to be of childbearing potential if she is postmenopausal, defined by amenorrhea of ≥12 months duration and age ≥45 years, or has undergone hysterectomy and/or bilateral oophorectomy.

  The following are considered highly effective forms of contraception: 1) true abstinence; 2) male sterilization (with post-procedure documentation of absence of sperm in the ejaculate). For female patients, the sterilized male partner should be the sole partner.

  The following are considered effective forms of contraception: 1) intrauterine device (IUD; copper IUD or hormonal IUDs only) or intrauterine system; 2) condom with spermicidal foam/gel/film/cream/suppository; 3) occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.

  Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S*,* DCDS4501A*,* rituximab, *or obinutuzumab* (whichever is later).

4.1.2 <u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

- Prior use of any MAb, radioimmunoconjugate or ADC within 4 weeks before Cycle 1, Day 1
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational anti-cancer agent within 2 weeks prior to Cycle 1, Day 1

  Adverse events except for sensory neuropathy from any previous treatments must be resolved or stabilized to Grade ≤2 prior to Cycle 1, Day 1.
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1, Day 1
- Prior allogeneic stem cell transplant
- Eligibility for autologous SCT (patients with relapsed or refractory DLBCL)
- History of transformation of indolent disease to DLBCL
- History of severe allergic or anaphylactic reactions to MAb therapy (or recombinant antibody-related fusion proteins)

- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma (e.g., of the cervix or breast) are allowed. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥ 2 years prior to Cycle 1, Day 1.

- Current or past history of CNS lymphoma
- Current Grade > 1 peripheral neuropathy
- Evidence of significant, uncontrolled, concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Recent major surgery within 6 weeks prior to Cycle 1, Day 1, other than for diagnosis
- Presence of positive test results for hepatitis B (HBsAg and/or total anti-HBc) or hepatitis C (HCV antibody)

  Patients who are positive for anti-HBc are eligible only if PCR is negative for HBV DNA and it is believed by both the investigator and Medical Monitor that it is in the patient's best interest to participate.

  Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.

- Known history of HIV seropositive status
- Women who are pregnant or lactating
- Ongoing corticosteroid use > 30 mg/day prednisone or equivalent

  Patients receiving corticosteroid treatment ≤ 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor via facsimile and obtain the Sponsor's approval to enroll the patient. Once the Sponsor reviews and approves the patient for enrollment, the patient number will be assigned via IXRS.

As described in Section 3.1.1.2, only select investigator sites that have agreed to participate in the non-randomized *(Cohorts C and D)* portion of the study will enroll patients into these cohorts. Cohorts C and D will be opened sequentially following completion of the randomized portion of the study for patients with FL.

For obinutuzumab-containing cohorts (Cohorts E, G, and H), patients with either relapsed or refractory follicular NHL or relapsed or refractory DLBCL will be enrolled. After the safety run-in stage for DCDS4501A at 1.8 mg/kg in combination with obinutuzumab, the patients will be enrolled into the dose-expansion portion with 40 patients in each histology group.

Personnel responsible for performing PK and ATA assays will receive participants' treatment assignments to identify appropriate PK and ATA samples to be analyzed in the appropriate corresponding assays.

4.3 STUDY TREATMENT

4.3.1 DCDT2980S and DCDS4501A

4.3.1.1 Formulation and Storage

a. DCDT2980S

DCDT2980S will be provided as a lyophilized powder in a single-use 20-cc vial. The solution for reconstitution is Sterile Water for Injection (SWFI), and the reconstitution volume is 2.6 mL to yield a final concentration of 20 mg/mL DCDT2980S in 40 mM L-histidine hydrochloride, 240 mM sucrose, and 0.02% polysorbate 20, pH 6.0.

Reconstituted DCDT2980S should be further diluted with sterile 0.9% NaCl to a total volume of 250 mL.

DCDT2980S vials must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. DCDT2980S should not be used beyond the expiration date provided by the manufacturer. Vial contents should not be frozen or shaken and should be protected from direct sunlight. After reconstitution, DCDT2980S vials may be stored at room temperatures (>8°C–25°C [>46°F–77°F]) for up to 4 hours or at refrigerated temperatures (2°C–8°C [36°F–46°F]) for up to 8 hours prior to use. Once DCDT2980S has been diluted with sterile 0.9% NaCl, the solution should be used within 4 hours at room temperature or within 8 hours at refrigerated temperature. Vials are intended for single use only; therefore, any remaining solution should be discarded.

For further details, refer to the DCDT2980S Investigator Brochure.

b. DCDS4501A

DCDS4501A is provided as a liquid formulation and contains no preservatives. Each single-use 20-cc vial is filled to deliver 100 mg of DCDS4501A. The drug product is formulated as 10 mg/mL DCDS4501A in 20 mM L-histidine acetate, 240 mM sucrose, 0.02% (w/v) polysorbate 20, pH 5.5.

DCDS4501A will be administered to patients intravenously via syringe pump with an IV infusion set containing a 0.22−µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight.

DCDS4501A vials must be refrigerated at 2°C−8°C (36°F−46°F) upon receipt until use. DCDS4501A vials may be stored at room temperature (> 8°C−25°C [46°F−77°F]) for up to 8 hours. DCDS4501A should not be used beyond the expiration date provided by the manufacturer. Vial contents should not be frozen or shaken and should be protected from direct sunlight. Vials are intended for single use only; therefore, any remaining solution should be discarded.

Once the DCDS4501A dose solution has been prepared, the solution should be used within 4 hours at room temperature (> 8 °C−25°C [46°F−77°F]) or within 8 hours refrigerated at 2°C−8°C (36°F−46°F). Because the drug product contains no preservatives, the Sponsor recommends using DCDS4501A in a syringe and extension set as soon as possible to reduce the risk of microbial contamination.

For further details, refer to the DCDS4501A Investigator Brochure.

4.3.1.2 Dosage and Administration

a. DCDT2980S-Specific Information

DCDT2980S will be administered to patients by IV infusion. Compatibility testing has shown that DCDT2980S is stable when diluted in polyvinyl chloride (PVC) bags to a concentration at or above 0.04 mg/mL in 0.9% NaCl diluent. The drug product will be delivered following dilution in 0.9% NaCl with a final DCDT2980S concentration determined based on dose and patient weight. The study drug will be diluted in a PVC bag and delivered using a 0.22 µm in-line filter on the IV infusion set.

Additional information/instructions regarding study drug administration will be provided in the Pharmacy Binder.

b. DCDS4501A-Specific Information

DCDS4501A will be administered to patients intravenously via syringe pump with an IV infusion set containing a 0.22 µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight. Compatibility testing has shown that DCDS4501A is stable both in syringes made of polypropylene (PP) and in standard extension sets with 0.22 µm in-line filter, when stored neat or diluted with 0.9% NaCl saline.

Additional information/instructions regarding study drug administration will be provided in the Pharmacy Binder.

c. General Information

The total dose of DCDT2980S and DCDS4501A for each patient will depend on the patient's weight within 96 hours prior to Day 1 of each cycle. The patient weight obtained during screening may be used for dose determination at all treatment cycles; if the patient's weight within 96 hours prior to Day 1 of a given treatment cycle differs by >10% from the weight obtained during screening, then the new weight should be used to calculate the dose.

For both DCDT2980S and DCDS4501A, the initial dose will be administered to well-hydrated (based on clinical judgment) patients over 90 ($\pm$10) minutes. Premedication with acetaminophen or paracetamol (e.g., 500–1000 mg) and diphenhydramine (e.g., 50°C–100 mg) per institutional standard practice may be administered prior to each infusion. Administration of corticosteroids is permitted at the discretion of the treating physician. Patients who do not receive premedications prior to the first dose of DCDT2980S and who develop an IRR during the first dose should receive premedications prior to subsequent doses (see Table 1).

The DCDT2980S/DCDS4501A infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. Following the initial dose, patients will be observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If the infusion is well-tolerated, subsequent doses of DCDT2980S/DCDS4501A may be administered over 30 ($\pm$10) minutes, followed by a 30-minute observation period post-infusion.

For instructions on study drug preparation and administration, refer to the DCDT2980S and DCDS4501A Investigator Brochure.

4.3.1.3 Dosage Modification

Patients should be assessed clinically for toxicity prior to each dose using the NCI CTCAE v4.0 grading scale. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable. If scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date, with subsequent dosing continuing on a 21-day schedule as applicable.

Specific guidelines around dosage modifications for neutropenia and peripheral neuropathy are detailed below in Sections 4.3.1.6 and 4.3.1.7. Patients who experience other treatment-related Grade 3 or 4 toxicity or laboratory abnormalities will be allowed to delay dosing of study treatment (both ADC and rituximab *or obinutuzumab*) for up to 2 weeks to allow for recovery. Patients may continue to receive additional infusions of DCDT2980S or DCDS4501A per their treatment assignment provided that the toxicity has resolved to Grade $\leq$2 or $\geq$80% of the baseline value, whichever is lower, within the

2–week delay period. Upon resolution, the dose for subsequent infusions may be reduced to 1.8 mg/kg *(in Cohorts C and D)*. If the toxicity that resulted in the dose reduction persists or recurs at the reduced dose, then the patient should be discontinued from study treatment. The decision for dose modification will be made on the basis of the investigator's assessment of ongoing clinical benefit with continued study treatment and in consultation with the Medical Monitor.

Once dose reductions of DCDT2980S or DCDS4501A are made for toxicity, dose re-escalation will not be allowed. Patients who are enrolled in the non-randomized portion of the study (Cohorts C and D), are dosed at an ADC dose of 1.8 mg/kg, and have progressive disease in the absence of any drug-related toxicity may have their ADC dose increased to 2.4 mg/kg if it is felt that there is reasonable justification for ongoing clinical benefit. The decision to increase the dose must be made in consultation with and approval of the Medical Monitor. *Patients in Cohorts E, G, and H (obinutuzumab-containing cohorts) will not be eligible for dose escalation.*

If a patient develops unacceptable toxicity to DCDT2980S or DCDS4501A, requiring its discontinuation, single-agent rituximab may be continued on the basis of the investigator's assessment of ongoing clinical benefit and with the approval of the Medical Monitor. *Patients enrolled in obinutuzumab-containing cohorts will not continue on single-agent obinutuzumab unless approved by the Medical Monitor.*

4.3.1.4 Schedule Modification

Patients in whom toxicities have not resolved to Grade ≤ 2 or $\geq 80\%$ of baseline value, whichever is lower, may have their study treatment delayed by up to 2 weeks. Dosing of both DCDT2980S or DCDS4501A and rituximab *or obinutuzumab* should be held during this period. If all study drug–related toxicities have resolved sufficiently, the patient may resume DCDT2980S or DCDS4501A and rituximab *or obinutuzumab* dosing on the regular every-21-day schedule.

A patient's dosing may be changed to a 28-day cycle if it is felt by the investigator that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from a transient and reversible toxicity—for example, cytopenia without requiring repeated treatment delays. Modifications to the dosing schedule in this fashion must be made in consultation with and with the approval of the Medical Monitor.

Patients who do not fulfill the criteria for continuation of dosing after the 2-week delay may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.6). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

Specific guidelines around schedule modifications for neutropenia and peripheral neuropathy are detailed below in Sections 4.3.1.6 and 4.3.1.7.

4.3.1.5 Infusion Reaction

Patients will be monitored during and after each DCDT2980S/DCDS4501A infusion for 90 minutes after the first infusion and for 30 minutes after subsequent infusions in the absence of infusion-related adverse events. Patients who experience infusion-related symptoms should be managed as described in Table 1. Precautions for suspected anaphylactic reaction during study drug infusions are provided in Appendix D.

In the event of a life-threatening IRR, which may include pulmonary or cardiac events, or an IgE-mediated anaphylactic reaction, administration of DCDT2980S/DCDS4501A should be immediately discontinued. Patients who experience these reactions should receive aggressive symptomatic treatment and are not eligible to receive any additional study treatment.

Premedication prior to DCDT2980S/DCDS4501A with acetaminophen/paracetamol, antihistamines, or corticosteroids per standard clinical practice is permitted—for example, in patients with substantial tumor burden and where the risk of cytokine release syndrome is high. In patients who do not receive premedication prior to any given dose of DCDT2980S/DCDS4501A and who develop any Grade ≥ 2 infusion-related toxicity, premedication should be administered prior to subsequent doses.

Table 1 Management of Infusion-Related Symptoms *for All Study Drugs*

Infusion-Related Symptoms [a]	Guidance
Grade 1–2	• Slow or hold infusion • Give supportive treatment [b] • Upon symptom resolution, may resume/escalate infusion rate at the investigator's discretion [c] • Note: For Grade 2 wheezing or bronchospasm, patient must be premedicated for subsequent doses. If symptoms recur with the same or greater severity, the infusion must be stopped immediately and study treatment permanently discontinued.
Grade 3	• Discontinue infusion • Give supportive treatment [b] • Upon symptom resolution, may resume/escalate infusion rate at the investigator discretion [c] • Note: If *the same adverse event recurs* with the same or greater severity, treatment *must be* permanently discontinued. • *Note: For Grade 3 hypotension or fever, patient must be premedicated before re-treatment. If symptoms recur, then study drug must be permanently discontinued.* • *Note:* If patient has Grade 3 wheezing or bronchospasm at first occurrence, study treatment should be permanently discontinued.
Grade 4	• Discontinue infusion immediately, treat symptoms aggressively, and permanently discontinue patient from study treatment

IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Refer to the NCI CTCAE v4.0 scale for the grading of symptoms. Management of IgE-mediated allergic reactions should be as directed in the text *preceding* this table.

[b] Supportive treatment: Patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the last 4 hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators. Patients with hypotension requiring vasopressor support must be permanently discontinued from study drug.

[c] Infusion rate escalation after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hr every 30 minutes.

4.3.1.6 Neutropenia

Because neutropenia is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.3.3), the use of growth factor support (G-CSF) as prophylactic and therapeutic indications is permitted (see Appendix F) in order to allow continued dosing of DCDT2980S/DCDS4501A. Dose modifications for patients who experience treatment-related Grade 3–4 neutropenia in the context of G-CSF usage are as follows:

- Primary prophylaxis with G-CSF (i.e., prior to the first dose of DCDT2980S/DCDS4501A) is permitted for patients with clinical factors listed in Appendix F or who otherwise are considered at high risk for developing neutropenia on study treatment.
- Patients who experience treatment-related Grade 3–4 neutropenia will be allowed to delay dosing of study treatment (both ADC and rituximab *or obinutuzumab*) for up to two weeks to allow for recovery. Therapeutic G-CSF is permitted as clinically indicated (see Appendix F) and to facilitate neutrophil recovery to allow subsequent DCDT2980S/DCDS4501A dosing.
- Subsequent dosing of DCDT2980S/DCDS4501A *and rituximab/obinutuzumab* is permitted provided that the neutropenia has resolved to Grade ≤ 2 or $\geq 80\%$ of the baseline value, whichever is lower, within the 2-week period.
- If prophylactic G-CSF was not administered prior to the cycle in which the Grade 3–4 neutropenia developed, then prophylactic G-CSF may be administered prior to subsequent cycles without DCDT2980S/DCDS4501A dose reduction. The dose schedule may be changed from 21-day to 28-day cycles to provide sufficient time for neutrophil recovery in subsequent cycles. In the absence of prophylactic G-CSF or dose schedule modification, the dose of DCDT2980S/DCDS4501A in subsequent cycles should be reduced to 1.8 mg/kg. *For Cohorts E, G, and H, patients will be given DCDS4501A at a dose of 1.8 mg/kg, and further dose reductions cannot be made.*
- If Grade 3–4 neutropenia recurs with prophylactic G-CSF, the dose for subsequent DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg. Prophylactic G-CSF and dose schedule modifications as described above are permitted in order to maintain the reduced DCDT2980S/DCDS4501A dose level and schedule.
- If Grade 3–4 neutropenia recurs at the reduced dose despite the administration of prophylactic G-CSF, then the patient should be discontinued from study treatment.
- For patients enrolled into the non-randomized portion of the study (Cohorts C and D*, as well as Cohorts E, G, and H*), dose modifications will not be allowed. Administration of therapeutic/prophylactic G-CSF and dose-schedule modifications as described above are allowed. Patients who have persistent or recurrent Grade 3–4 neutropenia as defined above should be discontinued from study treatment.

The determination of the dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment and with the approval of the Medical Monitor.

4.3.1.7 Peripheral Neuropathy

Peripheral neuropathy *(sensory or motor)* is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.2.5). For new or worsening drug-related Grade 2 or 3 peripheral sensory *and/or motor* neuropathy, dosing should be held for up to 2 weeks until peripheral neuropathy *(sensory or motor)* improves to Grade 1 or baseline grade. Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and approval of the Medical Monitor based on an assessment of the benefit-risk analysis of continuing to delay study treatment.

Following resolution of peripheral neuropathy *(sensory and/or motor)*, subsequent doses of DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg. *DCDS4501A should not be reduced to a dose lower than 1.8 mg/kg.* If worsening Grade 2 or 3 peripheral neuropathy *(sensory and/or motor)* recurs following dose reduction, study treatment should be discontinued. For Grade *3* peripheral neuropathy *(sensory and/or motor)*, study treatment should be discontinued.

For patients enrolled into the non-randomized portion of the study (Cohorts C and D), dose modifications will not be allowed. Patients who have Grade 2 or 3 peripheral neuropathy *(sensory and/or motor),* as defined above*,* should be discontinued from study treatment.

4.3.1.8 Hyperglycemia

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other ADCs using the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation of improved anti-hyperglycemic medications (see Section 3.4.3.7).

For symptomatic fasting Grade 3 (>250–500 mg/dL) or asymptomatic Grade 4 (>500 mg/dL) hyperglycemia, medical management should be initiated immediately and consultation with a specialist should be considered. If the hyperglycemia persists for >1 week after initiation of management, dose modification, schedule modification, or discontinuation of study treatment should be considered. In these cases, the study Medical Monitor should be consulted to assess the benefit-risk balance of continued study treatment.

4.3.2 Rituximab

4.3.2.1 Formulation

Rituximab (Rituxan®/MabThera®) is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in 500-mg (50-mL) single-use vials. A single-unit, 500-mg carton contains one 50-mL vial of rituximab (10 mg/mL). The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, and 0.7 mg/mL polysorbate 80, after reconstitution with SWFI. The pH is adjusted to 6.5. Vials are for

single use. Each vial and carton will contain a label (either single-panel or booklet) affixed to the vial or carton.

4.3.2.2 Dosage, Administration, and Storage

Rituximab (Rituxan®, MabThera®) will be administered intravenously once per 3-week (or 4-week) cycle. The infusion at 375 mg/m^2 for each dose will be based on the patient's body surface area at screening and will remain the same throughout the study.

If a scheduled dose of rituximab falls outside of the ±2-day window for reasons other than an adverse event, the site must notify and have a discussion with the Genentech Medical Monitor prior to rituximab administration. Such dosing may not necessarily qualify as a protocol deviation, if deemed to be in the best interests of the patient, after consultation with the Medical Monitor and agreed to in advance by the Medical Monitor.

Rituximab should not be administered as an IV push or bolus. Infusion reactions may occur. Premedication consisting of acetaminophen (or paracetamol), diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (e.g., up to 100 mg or an equivalent dose of methylprednisolone) may also be administered beginning with the first infusion, per standard clinical practice. Premedication may attenuate infusion reactions. Because transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

a. First Infusion

The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If infusion reactions do not occur, the infusion rate should be escalated in 50–mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

b. Subsequent Infusions

If the patient tolerates the first infusion well, subsequent rituximab infusions may be administered at an initial rate of 100 mg/hr and increased in 100–mg/hr increments at 30-minute intervals to a maximum of 400 mg/hr, as tolerated. If the patient does not tolerate the first infusion well, the guidelines for the first infusion should be followed.

If a patient tolerates the first three cycles of study treatment without significant infusion reactions, rituximab may be administered as "rapid infusion" in accordance with local institutional guidelines.

c. Storage

Rituximab vials must be stored at 2°C–8°C (36°C–46°F). Rituximab vials should be stored in the outer carton in order to protect them from light. Rituximab solution for

infusion may be stored at 2°C–8°C (36°C–46°F) for 24 hours and has been shown to be stable for an additional 12 hours at room temperature. However, because rituximab does not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between rituximab and PVC or polyethylene (PE) bags have been observed.

See the Rituxan® (Rituximab) Package Insert or SmPC (in the European Union) for additional information.

4.3.2.3 Dosage Modification

There will be no rituximab dose modification in this study. Patients at high risk for TLS complications (see Section 3.4.3.2) may, at the investigator's discretion, receive their initial dose of rituximab over 2 consecutive days (e.g., 125 mg/m^2 on Day 1, 250 mg/m^2 on Day 2; with DCDT2980S/DCDS4501A dose potentially delayed to Day 3).

Any NCI CTCAE (v4.0) toxicity Grade ≥ 3 in severity that is deemed related to rituximab treatment will require interruption of study treatment (both ADC and rituximab) until resolution to Grade ≤ 2 or $\geq 80\%$ of baseline, whichever is lower. Resumption of rituximab treatment may be considered in patients with resolution of toxicities to Grade ≤ 1 within 2 weeks at the discretion of the investigator, after consultation with the Medical Monitor. Failure of such toxicities to resolve after 2-week delay in study treatment will require permanent discontinuation of rituximab. Continuation of rituximab treatment may be permitted on the basis of ongoing clinical benefit following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

If a patient develops unacceptable toxicity to rituximab requiring its discontinuation, single-agent DCDT2980S or DCDS4501A may be continued on the basis of the investigator's assessment of ongoing clinical benefit and with the approval of the Medical Monitor.

4.3.2.4 Schedule Modification

Patients in whom toxicities have not resolved (i.e., to Grade ≤ 1 or $\geq 80\%$ of baseline) may have their study treatment delayed by up to 2 weeks. If after the up to–2-week delay, all study drug–related toxicities have resolved sufficiently, the patient may receive the scheduled doses of rituximab. In addition, a patient's dosing may be changed to a 28-day cycle if it is felt by the investigator and Medical Monitor that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from transient cytopenias without requiring repeated treatment delays.

Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.1). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by

the investigator and approval from the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

4.3.2.5 Infusion Reaction

Patients will be monitored during and after each rituximab infusion for 90 minutes after the first infusion and for 30 minutes after subsequent infusions in the absence of infusion-related adverse events. Patients who experience infusion-related symptoms should be managed as directed in Table 1 (see Section 4.3.1.5).

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction to rituximab, rituximab should be discontinued and no additional rituximab should be administered. Patients who experience these reactions should receive aggressive symptomatic treatment and should be discontinued from study treatment.

4.3.3 *Obinutuzumab*

4.3.3.1 *Formulation*

Obinutuzumab (GA101/Gazyva™/Gazyvaro) is a clear, colorless to slightly brownish liquid, provided as a single 1000-mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50–mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188, and highly purified water (HPW).

4.3.3.2 *Dosage, Administration and Storage*

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg in combination with DCDS4501A, as outlined in Section 3.1.3. Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–8 (see Table 2). No dose modifications of obinutuzumab are allowed.

All obinutuzumab infusions should be administered after premedication with oral acetaminophen and an antihistamine (see Section 4.4.1). The prophylactic use of corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) may also be considered for patients thought to be at high risk for IRRs, if deemed appropriate by the investigator, and should be administered prior to the obinutuzumab infusion. On Cycle 1 Day 1, it is recommended that oral prednisone, prednisolone, or methylprednisolone be given within 12 hours as a premedication but at least 60 minutes prior to the obinutuzumab infusion. Premedication with prednisone or prednisolone is mandatory in patients who had an IRR and should continue until IRRs no longer occur during antibody infusion. For the management of IRRs and anaphylaxis, see Table 1 (Section 4.3.1.5).

If it is the strong preference of the investigator or of the site (e.g., for logistical reasons) or if the patient is at increased risk for an IRR (high tumor burden, high peripheral

lymphocyte count), the administration of obinutuzumab infusion can be split over 2 days.

Table 2 Administration of First and Subsequent Infusions of Obinutuzumab

First Infusion (Cycle 1 Day 1)	*Subsequent Infusions*
• *Begin infusion at an initial rate of 50 mg/hr.* • *If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/hour increments every 30 minutes to a maximum of 400 mg/hr.* • *If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate used at the time the reaction occurred).*	• *If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, use full premedication including 100 mg prednisone/prednisolone (until no further IRR occurs), begin infusion at an initial rate of 50 mg/hr, and follow instructions for first infusion.* • *If the patient tolerated the prior infusion well (defined by absence of Grade 2 reactions during a final infusion rate of ≥100 mg/hr), begin infusion at a rate of 100 mg/hr.* • *If no reaction occurs, increase the infusion rate in 100-mg/hour increments every 30 minutes, to a maximum of 400 mg/hr.* • *If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate used at the time the reaction occurred).*

IRR =infusion-related reaction.

In all parts of the study, obinutuzumab must be administered in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available, and patients should be under the close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Table 1 (Section 4.3.1.5).

Obinutuzumab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. Administration sets with PVC, polyurethane (PUR), or PE as a product contact surface and IV bags with polyolefin (PO), polypropylene (PP), PVC, or PE as a product contact surface are compatible and can be used. Do not use an additional in-line filter because of potential adsorption.

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For clinical formulation-specific and batch-specific instructions and information on in-use stability, see the packaging label.

4.3.3.3 *Dosage Modification*

There will be no obinutuzumab dose modification in this study. Patients at high risk for TLS complications (see Section 3.4.2.2) may, at the investigator's discretion, receive obinutuzumab over 2 consecutive days (with DCDS4501A dose potentially delayed to Day 2 or Day 3).

Any NCI CTCAE (v4.0) toxicity Grade ≥3 in severity that is deemed related to obinutuzumab treatment will require interruption of study treatment (both DCDS4501A and obinutuzumab) until resolution to Grade ≤2 or ≥80% of baseline, whichever is lower. Resumption of obinutuzumab treatment may be considered in patients with resolution of toxicities to Grade ≤1 within 2 weeks at the discretion of the investigator, after consultation with the Medical Monitor. Failure of such toxicities to resolve after 2-week delay in study treatment will require permanent discontinuation of obinutuzumab. Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and approval of the Medical Monitor based on an assessment of the benefit-risk analysis of continuing to delay study treatment.

If a patient develops unacceptable toxicity to obinutuzumab requiring its discontinuation, single-agent DCDS4501A will not be permitted.

4.3.3.4 *Schedule Modification*

Patients in whom toxicities have not resolved (i.e., to Grade ≤1 or ≥80% of baseline) may have their study treatment delayed by up to 2 weeks. ***Dosing of both DCDS4501A and obinutuzumab should be held during this period.*** *If all study drug–related toxicities have resolved to Grade ≤1 or ≥ 80% of baseline, the patient may resume DCDS4501A and obinutuzumab dosing on the regular every–21–day schedule. In addition, a patient's dosing may be changed to a 28-day cycle if it is felt by the investigator and Medical Monitor that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from transient cytopenias without requiring repeated treatment delays.*

Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.6). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

Specific guidelines around schedule modifications for thrombocytopenia are detailed below in Section 4.3.3.5.

4.3.3.5 *Thrombocytopenia*

Thrombocytopenia is a known risk of obinutuzumab (see Section 3.4.6.4). If the clinical condition of a patient requires the use of concomitant anticoagulants, the patient is at increased risk of bleeding when the platelet count is <20,000/μL. When possible, replace prior therapy with Vitamin K antagonists, such as warfarin, with low-molecular weight heparin (LMWH) or new oral anticoagulants (NOACs) before Cycle 1 Day 1. Clinical decision making may be adjusted depending on the patient-specific assessment of benefit and risk.

In the event of severe thrombocytopenia (platelet count <10,000/μL) and/or symptomatic bleeding (irrespective of platelet count) in patients who are not receiving concomitant anticoagulants or platelet inhibitors:

- *Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves, but do not skip any doses of obinutuzumab for the sake of maintaining the study treatment schedule.*

In the event of thrombocytopenia with platelet count <20,000/μL and/or symptomatic bleeding (irrespective of platelet count) in patients who are receiving concomitant anticoagulants or platelet inhibitors:

- *Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves, but do not skip any doses of obinutuzumab for the sake of maintaining the study treatment schedule.*
- *For patients who are on LMWH or NOACs, when platelet count <20,000/μL develops, reduce the dose of LMWH or NOACs used.*
- *For patients who are on platelet inhibitors when thrombocytopenia with platelet count <20,000/μL develops, consideration should be given to temporarily pausing the use of platelet inhibitors.*

4.3.4 *Investigational Medicinal Product Accountability*

All investigational medicinal products (IMPs) required for completion of this study (pinatuzumab vedotin [DCDT2980S], polatuzumab vedotin [DCDS4501A], rituximab, and obinutuzumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will be either disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Concomitant Therapy

Concomitant therapy includes any *medication (e.g.,* prescription *drugs,* over-the-counter *drugs, herbal or homeopathic remedies, and nutritional supplements)* used by a patient *from* 7 days *prior to* the screening evaluation *to* the end of study visits. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF). Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Concomitant use of hematopoietic growth factors is allowed in accordance with instructions provided in the package inserts.

Patients who experience infusion-related temperature elevations of $>$38.5°C ($>$ 101.3°F) or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol ($\geq$ 500 mg) and/or H1 and H2 histamine-receptor antagonists (e.g., diphenhydramine, ranitidine). Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with additional supportive therapies (e.g., supplemental oxygen, β2-agonists, and/or corticosteroids) as clinically indicated according to standard clinical practice (see Table 1).

For patients enrolled on obinutuzumab-containing regimens, it is recommended that oral prednisone, prednisolone, or methylprednisolone be given as premedication within 12 hours of, but at least 60 minutes prior to, the obinutuzumab infusion on Cycle 1 Day 1. After the first obinutuzumab infusion, additional glucocorticoids are allowed at the investigator's discretion. For patients who did not experience infusion-related symptoms with their previous infusion, premedication at subsequent infusions may be omitted at the investigator's discretion.

Infusion reaction prophylaxis with medications (e.g., acetaminophen/paracetamol, antihistamines, and/or corticosteroids) may be instituted at any point in the study if it is determined to be in the best interest of the patient on the basis of the observation of IRRs in patients already enrolled in the study. Patients with Grade 3 hypotension or fever must be premedicated prior to retreatment (see Section 4.3.1.5). Patients with hypotension requiring vasopressor support or with Grade 3 wheezing, hypoxia, or generalized urticaria must be permanently discontinued from study treatment.

4.4.2 Excluded Therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy
- Immunotherapy including immunosuppressive therapy
- Radioimmunotherapy

- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Biologic agents (other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts); guidelines for the use of G-CSF are detailed in Section 4.3.1.6 and Appendix F.
- Any therapies intended for the treatment of lymphoma or leukemia, whether approved by local regulatory authorities or investigational

Patients who require the use of any of these agents will be discontinued from all study treatment. Patients who are discontinued from study treatment will be followed for safety outcomes for 30 days following the patient's last dose of DCDT2980S or DCDS4501A or rituximab *or obinutuzumab*, whichever is later, or until the patient receives another anti-cancer therapy, whichever occurs first.

4.5 STUDY ASSESSMENTS

4.5.1 Definitions of Study Assessments

4.5.1.1 Medical History and Demographics

Medical history includes all clinically significant diseases, prior cancer history, prior cancer therapies and procedures, and all medications used by the patient within 7 days preceding the screening visit.

4.5.1.2 Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure while the patient is in a sitting or semi-supine position, pulse oximetry, pulse rate, and body temperature. Every effort will be made to ensure that vital signs are obtained from patients in a consistent manner and position. The timing of vital sign collection on the days of study treatment administration is as follows:

- For the administration of rituximab *or obinutuzumab*, vital signs should be assessed prior to the start of the infusion, every 15 (±5) minutes during the first hour of the infusion, as clinically indicated during the remainder of the infusion, and following the completion of the infusion.
- For the administration of DCDT2980S or DCDS4501A, vital signs should be assessed prior to the start of the infusion, every 15 (±5) minutes during the infusion, at the end of the infusion, and every 30 (±10) minutes for 90 minutes post-infusion following dosing at Cycle 1 and 30 (±10) minutes following dosing in subsequent cycles.

Additional monitoring of vital signs should be performed if clinically indicated.

4.5.1.3 Physical Examination

A complete physical examination should include the evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Targeted physical examinations should be limited to systems of clinical relevance (i.e., cardiovascular, respiratory, and any system that might be associated with tumor assessment, such as lymph nodes, liver, and spleen) and those systems associated with symptoms.

Changes from baseline should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

Resolution or any change in grade of peripheral neuropathy AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV). This also applies to AEs for which study drug was discontinued or for patients in the follow-up phase after last dose of study treatment with either ongoing AEs or new onset of an AE. For the AEs referring to the follow-up phase newly initiated, relevant treatments need to be documented with treatment dates.

4.5.1.4 Laboratory Assessments

On days of study drug administration, pre-infusion laboratory samples should be drawn within 4 hours prior to the start of infusion, unless otherwise specified. Local laboratory assessments may be obtained up to 72 hours prior to the start of study treatment administration (see below and Section 4.5.3). Instruction manuals and supply kits will be provided for all central laboratory assessments.

Central Laboratory Assessments

Samples for flow cytometry, PK, bone marrow, and anti-DCDT2980S*,* anti-DCDS4501A, *or anti-obinutuzumab* antibody assessments will be sent to one or several laboratories or to Genentech for analyses (see Section 3.6). The following assessments will be conducted:

- Leukocyte immunophenotyping/flow cytometry (fluorescence-activated cell sorting [FACS] lymphocyte subsets)

  Whole-blood samples will be collected to analyze B-cell subsets ($CD19^+$), T-cell counts ($CD3^+$, $CD4^+$, $CD8^+$), and NK cell counts ($CD16^+$, $CD56^+$), by flow cytometry.

- ATA assays

  ATAs to DCDT2980S*,* DCDS4501A, *or obinutuzumab* will be determined at Genentech using a validated ELISA (see Section 4.9).

- PK *and PD* assays (see Section 4.5.1.6)
- A plasma sample *and blood samples* will be collected from patients for exploratory research as indicated in Section 4.5.1.9.
- For patients who sign the optional consent, a blood sample will be collected prior to the first dose of study treatment for exploratory research.
- Tumor tissue sample (archival or fresh) will be collected from patients for central pathologic review as described in Sections 4.1.1 and 4.5.1.9.

Local Laboratory Assessments

Samples for hematology, serum chemistry, liver function, and pregnancy will be analyzed at the study site's local laboratory. Local laboratory assessments may be obtained up to 72 hours prior to start of study treatment administration on Day 1 of the treatment cycle.

- Hematology: includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells)
- Coagulation: aPTT, PT, and INR
- Quantitative immunoglobulins (IgA, IgG, and IgM)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid
- Serum γ-glutamyl transpeptidase (GGT) levels will be required at screening only
- Hemoglobin A1c
- Viral serology and detection (screening assessment only and if clinically indicated)

  Hepatitis B (HBsAg and HBcAb; also HBV DNA by PCR if the patient is HBcAb positive)

  HCV antibody

- Pregnancy test

  For women of childbearing potential (see Section 4.1.2), a serum pregnancy test must be performed within 14 days prior to Cycle 1 Day 1.

  Urine pregnancy tests will be performed during the study treatment period. If any urine test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Any patient with a positive serum test will not be allowed to receive any study treatment.

4.5.1.5 Electrocardiogram Assessments

Twelve-lead digital ECG measurements will be obtained in triplicate, with immediately consecutive ECGs obtained until three evaluable ECGs are recorded, at the following timepoints:

- Screening
- 30–60 minutes before the start of DCDT2980S or DCDS4501A infusion in Cycle 1
- 30–60 minutes after the completion of DCDT2980S or DCDS4501A infusion in Cycle 1
- 30–60 minutes after the completion of DCDT2980S or DCDS4501A infusion in Cycle 3

- Day 8 (±1 day) of Cycle 3 time matched (i.e., obtained at the same time of day) with post-DCDT2980s/DCDS4501A infusion ECGs for Cycle 3 *only for rituximab-containing arms/cohorts*
- Treatment completion/early termination visit

Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of or suspicion for clinically significant signs or symptoms of cardiac dysfunction.

All ECGs as described above will be submitted to a Sponsor-designated ECG central laboratory for storage and potential analysis. Detailed instructions on ECG acquisitions and transmissions to the ECG central laboratory will be provided in the ECG manual provided for this study.

Representative ECGs at each timepoint should be reviewed by the investigator or a qualified designee. Post-screening ECG measurements should be obtained as close as possible to scheduled serum and plasma PK samples (see Appendices B-1 and B-2) and should be no more than 30 minutes apart. If QTc prolongation (>500 ms and >60 ms longer than the pre-dose baseline value) is noted, ECGs should be repeated until the prolongation is reversed or stabilized. If a PK sample is not scheduled at the timepoint where QTc prolongation is first observed, then an unscheduled sample should be obtained. An evaluation for potential causes of QT prolongation—for example, electrolyte imbalances or concomitant medications—should be performed, study treatment dosing held, and the Medical Monitor notified. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician.

4.5.1.6 Pharmacokinetic *and Pharmacodynamic* Assessments

Pharmacokinetics of DCDT2980S and DCDS4501A will be characterized by measuring total antibody (conjugated and unconjugated antibody), acMMAE, and free MMAE concentrations using validated methods (see Section 4.9). Plasma samples may also be analyzed for other potential MMAE-containing catabolites, per sponsor's discretion. Pharmacokinetics of rituximab will be characterized by measuring rituximab concentrations using a validated method (see Section 4.9). *Pharmacokinetics of obinutuzumab will be characterized by measuring obinutuzumab concentrations with use of a validated method (see Section 4.9).* These assessments will allow for further characterization of pharmacokinetics of DCDT2980S and DCDS4501A, the assessment of the drug interaction potential when they are given in combination with rituximab *or obinutuzumab*, and the investigation of potential correlations between PK parameters and safety and/or activity if data allow and at the sponsor's discretion. *Pharmacodynamics of obinutuzumab and DCS4501A may be assessed by monitoring the release of tumor associated DNA following treatment.*

4.5.1.7 Immunogenicity Assessments

The immunogenicity evaluation will utilize a risk-based strategy and tiered approach (Rosenberg and Worobec 2004a, 2004b, 2005; Koren et al. 2008) designed to detect and characterize all ATA responses to DCDT2980S and DCDS4501A. Patient samples will first be screened to detect all antibody responses toward DCDT2980S or DCDS4501A. Samples that screen positive will be analyzed in a confirmatory assay (competitive binding with DCDT2980S or DCDS4501A) to assess the specificity of the positive response. Titers will be determined for confirmed positive samples. Further characterization will be assessed by competitive binding with the MAb component of DCDT2980S or DCDS4501A to characterize whether the ATA responses are primarily to the mAb or the linker-drug regions of the ADC. Positive ATA samples will be stored for further characterization of ATA responses, if necessary.

The schedule of sample collection for ATA assessment is outlined in Appendices B-1*,* B-2*, or B-3*, depending on the schedule of study treatment administration. Samples for ATA will not be collected during the crossover treatment period.

ATA responses to obinutuzumab will be detected and confirmed using a similar tiered approach. Patient samples will first be screened to detect all antibody responses to obinutuzumab. Samples that screen positive will be analyzed in a confirmatory assay (competitive binding with obinutuzumab) to assess the specificity of the positive response. The relative levels of ATA in confirmed positive samples will be determined in a titering assay. Positive ATA samples will be stored for further characterization of ATA responses, if necessary.

4.5.1.8 Tumor Response Assessments

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, on the basis of physical examinations, CT *scans, PET scans,* and/or MRI scans, and bone marrow examinations, using standard response criteria for NHL (Cheson et al. 2007) (see Appendix C-*1 and C-2*).

a. Radiographic Assessments *for Patients on Rituximab-Containing Arms/Cohorts*

CT scans with contrast should include chest, abdomen, and pelvis scans; CT scans of the neck should be performed at screening and followed only if disease is present at screening. Post-screening radiographic assessments may be limited to areas of prior involvement only if required by local health authorities.

MRI scans may be used instead of CT scans in patients for whom CT scans with IV contrast are contraindicated. Details regarding imaging procedures in these cases will be provided in the Imaging Manual.

An ^{18}F-fluorodeoxyglucose–positron emission tomography (^{18}F-FDG-PET) (hereafter referred to as PET) scan is required during screening for all patients with DLBCL. An additional PET scan in DLBCL patients should be obtained at the 6-month tumor assessment to ensure consistency of response assessment methodology at this timepoint for all patients. PET scans should additionally be obtained to confirm disappearance of metabolically active disease during study treatment and to confirm a CR upon discontinuation of study treatment.

For patients with FL, PET scans are not required but may be obtained on the basis of physician preference and if permitted by local health authorities. Similarly, for DLBCL, PET scans on patients with FL should be obtained during screening; for patients whose tumors are PET positive during screening, an additional PET scan should be obtained at the 6-month tumor assessment. PET scans should additionally be obtained to confirm disappearance of metabolically active disease during study treatment and to confirm a CR upon discontinuation of study treatment.

For all patients regardless of disease subtype, combined PET-CT scans may be used instead of CT alone if performed with contrast and if collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent PET-CT scans. If a PET-CT scan is to be used during screening, then PET-CT scans should be performed for all subsequent tumor assessments in order to ensure their consistency across different timepoints.

All tumor assessments will be submitted to an IRF for storage and possible independent centralized review. Details related to submission of data to the IRF will be defined in a separate Imaging Manual.

b. *Radiographic Assessments for Patients on Obinutuzumab-Containing Cohorts*

PET scans should minimally extend from skull-base to mid-thigh. Full-body PET scan should be performed when clinically appropriate.

CT scans with oral and IV contrast should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated. CT scans for response assessment may be limited to areas of prior involvement only if required by local health authorities. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

In patients for whom contrast is contraindicated—for example, patients with contrast allergy or impaired renal CL—CT or combined PET/CT scans without contrast are permitted so long as they permit consistent and precise measurement of target lesions during the study treatment period.

PET and CT scans are required for follicular NHL and DLBCL patients at screening, after Cycle 4 of study treatment (i.e., between Cycle 4 Day 15 and Cycle 5 Day 1), and at EOT. The EOT response assessment should be performed 6–8 weeks after Cycle 8 Day 1 or last study treatment. CT scans without PET scans will be obtained every 3 months for 1 year, then every 6 months for 1 year, for a total of approximately 2 years after the treatment completion visit, with use of standard response criteria for NHL (see Appendix C-2).

c. Bone Marrow Assessments

A bone marrow biopsy for morphology is required at screening and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated.

d. Schedule of Tumor Response Assessments *for Rituximab-Containing Arms/Cohorts*

Tumor response assessments will be performed every 3 months (±1 week) from the initiation of study treatment until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). The schedule of tumor assessments *is* independent of the study treatment dose schedule. *For patients enrolled on rituximab-containing arms/cohorts,* the schedule of tumor response assessments is detailed in Appendix A-1. As stated above, for all DLBCL patients *enrolled on a rituximab-containing arm/cohort*, PET scans are required during the screening period and at the 6-month tumor assessment timepoint.

The schedule for tumor response assessments for patients who proceed to crossover treatment is detailed in Appendix A-2.

Additional response assessments, after the final dose of study treatment, for patients who discontinue from study treatment (either initial or crossover treatment) for reasons other than progressive disease, will be performed as described in Appendix A-*4*.

Tumor assessments should also be performed within 30 days after the last study drug infusion (both initial and crossover treatment) at the treatment completion/early termination visit. Imaging scans are not required at the treatment completion/early termination visit if scans have been performed within the previous 8 weeks or if disease progression while receiving study treatment is documented.

If, at any time during the study, disease progression is suspected, a tumor assessment must be performed.

e. Schedule of Tumor Response Assessments for Obinutuzumab-Containing Cohorts

All follicular NHL and DLBCL patients enrolled in obinutuzumab-containing cohorts are required to have a combined PET and CT scan at screening, after Cycle 4 of treatment, and at EOT. The schedule for tumor response assessments for patients enrolled on obinutuzumab-containing cohorts is detailed in Appendix A-3.

4.5.1.9 Exploratory Research

a. Tumor Tissue Samples

Required Tumor Tissue Samples

Tumor tissue samples will be used for central pathologic laboratory review of CD20, CD22, and CD79b expression. Additional studies to fulfill the exploratory objectives in Section 3.3.4 will be performed, including, but not limited, to the following:

- Messenger RNA (mRNA) expression profiling for signatures of NHL biology, including prognostic subpopulations (Alizadeh et al. 2000; Wright et al. 2003), target expression (CD20, CD22 and CD79b), and apoptotic response
- Tissue microarrays (TMAs) from cores taken from provided blocks for immunohistochemistry (IHC) and in situ hybridization (ISH) assessments *for* biomarker endpoints involved in response to chemotherapy including quantitation of Bcl-2 protein and genetic alterations of bcl-2 including gene rearrangements, amplifications, and t(14;18) translocations. Additional IHC markers may include those related to the tumor microenvironment.
- Tumor DNA to assess mutations that have been shown to be associated with NHL biology and activation of the B-cell receptor, including mutations in CD79b (Pasqualucci et al. 2011)

For patients who develop progressive disease and are eligible to receive crossover treatment (see Section 3.1.8), a biopsy of a safely accessible site of disease will be performed. Tumor tissue samples obtained at this timepoint will be used to assess changes in biology, target expression, and regulators of apoptosis as described above, which have occurred and may be linked to progression on initial study treatment.

Optional Tumor Tissue Samples (Requires Optional Research Informed Consent

For patients who provide informed consent, an optional tumor biopsy will be collected at time of progression from the following patients:

- Patients who develop disease progression following initial study treatment and do not proceed to receive crossover treatment
- Patients who develop disease progression on crossover treatment

Tumor tissue samples obtained at these timepoints will be used to assess changes in biology, target expression, and regulators of apoptosis, as described above, that have occurred and may be linked to progression on treatment.

b. Blood and Plasma Samples

A plasma sample will be collected prior to treatment.

Blood samples will be taken aligned with PK sampling to assess the pharmacodynamics response by monitoring circulating tumor DNA.

For patients who sign the Optional Research Informed Consent, an additional blood sample will also be taken prior to treatment.

The plasma and blood samples may be used for the assessment of specific tumor biologic markers, including proteins, circulating DNA, and microRNAs. The information obtained from these samples will enable a better understanding of the biology of NHL and disease prognosis, identify potential predictors of response to treatment with DCDT2980S, DCDS4501A, rituximab, *and/or obinutuzumab*, improve diagnostic assessments, and identify and characterize mechanisms of resistance to DCDT2980S or DCDS4501A and rituximab *or obinutuzumab* activity.

Because tumorigenesis is a multiple-step process linked to somatic events, any DNA analysis will focus on sporadic mutations specifically found in tumor tissue and not on inherited changes found in the whole body. For this purpose, some tumor-containing sections may be taken from the tissue block and used for the DNA extraction process. Assays on stored tissue samples may be performed at Genentech or at a central specialty laboratory.

4.5.1.10 Patient-Reported Outcome*s*

The MDASI (Cleeland et al., 2000; Appendix E) is a multi-symptom *self-report* measure for clinical and research use. The MDASI's 13 core-symptom items, plus an additional 4 items, for a total of 17 symptom items, include those found to have the highest frequency and/or severity in patients with various cancers and treatment types. These include pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling. Six additional items focus on the degree of interference of the aforementioned symptoms for a total of 23 items in the questionnaire.

PRO data will be elicited from all patients in this study to more fully characterize the clinical profile of study treatment. The MDASI PRO instrument will be supplied in the local language of each participating country. Electronic (handheld computers) will be used for the daily collection of symptoms derived from the MDASI.

4.5.2 Screening and Pretreatment Assessments

All screening evaluations must be completed and reviewed by the Genentech Medical Monitor or designated CRO Medical Monitor to confirm that patients meet all eligibility criteria and are approved for enrollment before the first infusion of study treatment. Written informed consent for participation in the study must be obtained before

performing any study-specific screening tests or evaluations. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site.

Screening and pretreatment tests and evaluations will be performed within 28 days preceding the day of the first dose of study treatment on Cycle 1 Day 1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 may be used; such tests do not need to be repeated for screening.

The availability of a patient's tumor tissue sample for studies (see Sections 4.1.1 and 4.5.1.9) should be confirmed prior to Cycle 1 Day 1. Such specimens should consist of representative core biopsy in a paraffin block, which is the preferred method, or at least 15 unstained slides. Tumor specimens should be submitted with an accompanying pathology report and may be obtained at any time prior to entry to study.

Bone marrow biopsy and aspirate specimens are required at screening (see Section 4.5.1.8). Unsuccessful attempts at obtaining marrow aspirates will not be considered a protocol deviation or violation.

Refer to the Study Flowchart provided in Appendix A-1 *and A-3* for the schedule of screening and pretreatment assessments.

4.5.3 Assessments during Treatment

Study drug infusions (rituximab*, obinutuzumab*, DCDT2980S, or DCDS4501A) should occur on the scheduled 21-day (or 28-day) cycle but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ±1 day from the scheduled date, unless otherwise noted. Study visits starting in Cycle 3 should occur within ±2 days from the scheduled date, unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed prior to study drug infusion unless otherwise noted.

Local laboratory assessments may be performed within 72 hours preceding study drug administration on Day 1 of each cycle. Otherwise, laboratory samples should be drawn 0–4 hours before infusion. Results must be reviewed and the review documented prior to study drug administration.

Refer to the Study Flowchart provided in Appendix A-1 for the schedule of treatment period assessments. *For patients enrolled in the obinutuzumab-containing cohorts, refer to the Study Flowchart provided in Appendix A-3.*

4.5.4 Study Treatment Completion Visit

Patients who complete study treatment or discontinue from study treatment early will be asked to return to the clinic within 30 days after the last DCDT2980S*,* DCDS4501A*,* rituximab, *or obinutuzumab* infusion (whichever is later) for a study treatment completion visit. The visit at which response assessment shows progressive disease may be used as the early termination visit.

Refer to the Study Flowchart provided in Appendix A-1 for assessments to be performed at the treatment completion/early termination visit. *For patients enrolled on the obinutuzumab-containing cohorts, refer to the Study Flowchart provided in Appendix A-3.*

Assessments conducted at the treatment completion/early termination visit may be used for the purposes of re-screening to determine eligibility to receive crossover treatment (see Section 3.1.3 and Section 4.5.5).

4.5.5 Crossover Treatment Completion Visit

Patients who fulfill the criteria to receive crossover treatment (see Section 3.1.6) will have assessments during the crossover treatment period as described in Appendix A-2. The same guidelines regarding scheduling of assessments for treatment with initial study treatment as detailed in Section 4.5.3 will apply to crossover treatment.

Patients who proceed to receive crossover treatment will have on-treatment assessments as described in Appendix A-2.

Patients who complete the crossover treatment (approximately 1 year/17 cycles) or discontinue from crossover treatment early will be asked to return to the clinic within 30 days after the last DCDT2980S, DCDS4501A, or rituximab infusion (whichever is later) for a crossover treatment completion/early termination visit. The visit at which response assessment shows disease progression on crossover treatment may be used as the early termination visit.

Refer to Appendix A-2 for assessments to be performed at the treatment completion/early termination visit.

4.5.6 Follow-Up Assessments

Ongoing adverse events thought to be related to DCDT2980S, DCS4501A, rituximab, *or obinutuzumab* will be followed until the event has resolved to baseline (pre-treatment) grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the adverse event.

Patients will be followed after the last dose of study treatment (either initial study treatment or crossover treatment) for safety outcomes. Such follow-up will require an assessment (per verbal report, at minimum) of any adverse events and serious adverse events for 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy, whichever occurs first.

4.5.6.1 *Follow-Up Assessments for Rituximab-Containing Regimens*

Patients who discontinue from study treatment (either initial study treatment or crossover treatment) for reasons other than progressive disease will be followed for response for up to 1 year after the last infusion of study treatment or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Response assessments should occur approximately every 2–3 months following the last infusions of DCDT2980S, DCDS4501A, or rituximab. Post-treatment assessments are described in Appendix A-*4*.

Following discontinuation of study treatment, patients will be followed for survival approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination.

4.5.6.2 *Follow-Up Assessments for Obinutuzumab-Containing Regimens*

Patients who discontinue from study treatment for reasons other than progressive disease will be followed for response for up to 2 years after the last infusion of study treatment or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Response assessments should occur approximately every 2–3 months following the last infusions of DCDS4501A or obinutuzumab for the first year after completion of treatment, then every 6 months for the second year after completion of treatment. Post-treatment assessments are described in Appendix A-5.

Following discontinuation of study treatment, patients will be followed for survival approximately every 6 months until death, loss to follow-up, withdrawal of consent, or study termination.

4.6 PATIENT DISCONTINUATION

4.6.1 Discontinuation from Treatment

Patients may discontinue study treatment early for reasons other than disease progression, such as patient/investigator choice or unacceptable toxicity. The reasons for early discontinuation of treatment must be documented on the appropriate eCRF. Patients may continue treatment with either DCDT2980S/DCDS4501A or rituximab alone following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

Patients who discontinue study treatment early due to toxicity should continue to be followed until resolution of toxicity as scheduled.

Refer to Sections 4.5.4 and 4.5.5 for assessments that are to be performed for patients who discontinue from the study during the study treatment period.

4.6.2 Discontinuation from Study

Patients must be discontinued from the study if they experience disease progression as defined using response and progression criteria in Appendix C. Patients can continue crossover treatment following documentation of the first progressive disease event but must be discontinued from the study if they experience a second progressive disease event on the crossover treatment.

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study, for reasons of noncompliance (e.g., missed doses or missed visits) or pregnancy or if the investigator determines it is in the best interest of the patient.

Refer to Sections 4.5.4 and 4.5.5 for assessments that are to be performed for patients who prematurely discontinue from the study during the treatment period.

4.7 STUDY DISCONTINUATION

Genentech has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

4.8 POST-TRIAL ACCESS

Genentech does not have any plans to provide DCDT2980S, DCDS4501A, rituximab*, obinutuzumab*, or other study interventions to patients after the conclusion of the study or if the study is terminated or for patients who withdraw early from the study or complete their study treatment. Genentech will evaluate the appropriateness of continuing to provide DCDT2980S, DCDS4501A, rituximab, *or obinutuzumab* to study patients after evaluating the safety and activity data from the study.

4.9 ASSAY METHODS

4.9.1 Total DCDT2980S/DCDS4501A Antibody ELISA

Total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) will be measured in serum samples using validated ELISAs.

4.9.2 Antibody-Conjugated MMAE (MMAE Affinity Capture Enzyme-Release LC/MS-MS)

acMMAE (a measure of MMAE conjugated to DCDT2980S/DCDS4501A) will be measured in plasma samples using validated affinity capture enzyme-release liquid chromatography–tandem mass spectrometry (LC-MS/MS) assays.

4.9.3 Free MMAE LC-MS/MS

Free MMAE will be measured in plasma samples using a validated electrospray LC-MS/MS method.

4.9.4 Rituximab ELISA

Rituximab will be measured in serum samples using a validated ELISA.

4.9.5 *Obinutuzumab ELISA*

Obinutuzumab will be measured in serum samples using a validated ELISA.

4.9.6 Anti-Therapeutic Antibody

ATAs against DCDT2980S and DCDS4501A in serum samples will be measured using validated bridging antibody ELISAs and characterized by competitive binding assays.

ATAs against obinutuzumab in serum samples will be measured using a validated bridging antibody ELISA.

4.9.7 Biomarker Assays

Tumor tissue assessment of biomarkers will be assayed using IHC, ISH, qPCR gene expression profiling using microarray *and* mutation detection assays. *Circulating Tumor DNA (ctDNA) in plasma samples will be assessed using a next generation sequencing approach (CAPP-Seq) to detect and quantitate lymphoma specific markers (Newman et al. 2014).*

4.10 STATISTICAL METHODS

The final analysis will be based on patient data collected *until all patients discontinue from the* study *or the study is terminated by the Sponsor*, whichever occurs first. The analyses will be based on the safety evaluable population, defined as patients who received at least one dose of study treatment. All summaries will be presented according to the disease-specific cohort, treatment group, and assigned dose level.

4.10.1 Analysis of the Conduct of the Study

Enrollment, major protocol violations, and reasons for discontinuations from the study will be summarized.

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, duration of malignancy, and baseline ECOG Performance Status, will be summarized

using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables. All summaries will be presented overall and by treatment group, assigned dose level, and disease-specific cohort.

Study drug administration data will be listed by the disease-specific cohorts described in Sections 3.1.1 and 3.1.2. Any dose modifications will be flagged. Means and standard deviations will be used to summarize the total doses of DCDT2980S, DCDS4501A*,* rituximab, *and obinutuzumab* received. All summaries will be presented by treatment group, assigned dose level, and disease-specific cohort.

4.10.2 Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, and changes in vital signs. All patients who receive any amount of DCDT2980S, DCDS4501A*,* rituximab, *or obinutuzumab* will be included in the safety analysis and will be assigned to the treatment group on the basis of the study treatment received. Patients who have dose level changes from the initial assigned dose level will be summarized by the initial assigned dose level of DCDT2980S or DCDS4501A.

All adverse event data will be listed by study site, patient number, treatment group, disease-specific cohort, and cycle. All adverse events occurring on or after treatment on Day 1 of Cycle 1 will be summarized by mapped terms, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade. In addition, all serious adverse events, including deaths will be listed separately and summarized.

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to DCDT2980S and DCDS4501A will be summarized.

4.10.3 Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum concentrations of total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) and rituximab *or obinutuzumab* and plasma concentrations of acMMAE and free MMAE versus time data will be tabulated and plotted by NHL disease subtype (relapsed or refractory follicular NHL or DLBCL). The pharmacokinetics of the above analytes will be summarized by estimating the appropriate PK parameters (e.g., AUC, C_{max}, CL, V_{ss}, and $t_{1/2}$). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and range). Non-compartmental, compartmental, and/or population methods will be used, as data allow.

Exposure-response (safety and efficacy) analysis may be conducted with use of PK data and available drug effect (e.g., imaging, measures of tumor burden) and toxicity (e.g., clinical pathology) data, at the sponsor's discretion.

In addition, population PK methods may be employed to manage sparse data and to investigate the effects of certain covariates on the pharmacokinetics of DCDT2980S and DCDS4501A, as data allow, and at the sponsor's discretion.

4.10.4 Activity Analyses

Best overall response, duration of response, and PFS will be listed for all patients.

ORR from the initial study treatment will be calculated on the basis of data from patients who received study treatment. Objective response is defined as CR or PR as determined by the investigator, on the basis of physical examinations, radiographic scans, and bone marrow examinations, using modified response criteria for NHL (Cheson et al. 2007; see Appendix C) and confirmed by repeat assessments ≥4 weeks after initial documentation. Any patient with insufficient data to determine response will be classified as a non-responder.

For patients with DLBCL, primary assessment of tumor response will be based on diagnostic imaging scans—for example, CT and/or MRI scans and PET scans. For patients with FL *enrolled on rituximab-containing arms/cohorts*, primary assessment of response will be based on CT scans only; the assessment of response in FL based on PET scans will be performed for exploratory purposes only.

For patients with DLBCL or FL on obinutuzumab-containing cohorts, primary assessment of tumor response will be based on PET/CT scans. Given the new Lugano Classification, 2014, criteria which recommend that complete response (PET-CR) be determined by PET-CT scan, patients in Cohorts E, G, and H will be evaluated with a PET-CT scan at screening, between Cycle 4 Day 15 and Cycle 5 Day 1, and at 6-8 weeks after completing treatment. The efficacy analysis for these cohorts will, therefore, be different from the analysis for Arms A-B and Cohorts C-D. (Cheson, et al 2014) (see Appendix C-2).

Among patients with an objective response, duration of response will be defined as the time from the initial *documentation of a* CR or PR to the time of disease progression or death. If a patient does not experience death or disease progression before the end of the study, duration of response will be censored at the day of the last tumor assessment.

For the randomized portion of the study (Arms A and B), PFS is defined as the time from the date of randomization to the date of disease progression or death from any cause, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the *date* of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. For the non-randomized portion of the study (Cohorts C *through H*), PFS is defined as the time from the date of study enrollment to the date of disease progression or death from any cause, whichever occurs first.

For the randomized portion of the study (Arms A and B), OS is defined as the time from the date of randomization to the date of death from any cause. For the non-randomized portion of the study (Cohorts C *through H*), OS is defined as the time from the date of study enrollment to date of death from any cause.

4.10.5 Exploratory Analyses

Assay results of possible predictive markers will be listed by treatment group and response status.

Summary statistics of the MDASI items, scales, and their changes from baseline will be calculated at each assessment timepoint. The mean, standard error, and median of the absolute scores and the mean changes from baseline (and 95% CI) within and between study arms will be reported for the MDASI scales and single items, as well as the weekly averages of the worst symptom rating. For change scores in the MDASI from baseline, patients without baseline scores will not be included in the analyses. Line charts depicting the means and mean changes of subscales over time will be also provided.

Frequencies and percentages of missing data for the PRO endpoints will be reported. Dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) will be summarized.

Repeated measures mixed-effects models will explore MDASI subscale scores with a baseline score and appropriate covariates added, as appropriate.

4.10.6 Handling of Missing Data

For the endpoint of objective response, patients without a post-baseline tumor assessment will be considered non-responders in the all-treated population analysis.

For duration of response and PFS, data from patients who are lost to follow-up will be included in the analysis as censored observations on the last date that the patient is known to be progression free, defined as the date of the last tumor assessment, or, if no tumor assessments were performed, as the date of last study treatment plus 1 day.

Compliance to PRO data collection will be reported with summary statistics, including frequencies of reasons for non-compliance such as patient refusal to complete PRO data collection.

4.10.7 Determination of Sample Size

For the randomized portion of the study (Arms A and B), a target of 120 patients will be enrolled in two separate cohorts of patients (40 in the follicular NHL cohort and 80 in the DLBCL cohort). *The randomized portion of this study is non-comparative in nature. No formal hypothesis testing is planned to compare the treatment arms. Moreover, there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms. Genentech has judged the proposed* sample size to provide sufficient

precision in estimating the anti-tumor activity of DCDT2980S combined with rituximab or DCDS4501A combined with rituximab as measured by objective response. For example, with the assumption of an observed response rate of 40%, a 90% confidence interval for the response rate would be approximately 22%–58% (i.e., 40% ± 18%) for the follicular NHL cohort and approximately 27%–53% (i.e., 40% ± 13%) for the DLBCL cohort. *With 40 patients, there is an 87% chance of observing at least one adverse event with a true incidence of 5%.*

For the non-randomized portions of the study (Cohorts C and D), approximately 20 patients will be enrolled into each arm, for a total of 40 patients. With 20 patients under an observed response rate of 40%, the exact Clopper-Pearson 90% confidence interval for the response rate would be 22%–61%. With respect to the assessment of safety based upon a sample size of 20 patients, the chance of observing at least one adverse event with a true incidence of 10% is 88%.

For the obinutuzumab safety run-in cohort (Cohort E), 6 patients will be enrolled. For the obinutuzumab expansion cohorts (Cohorts G and H), 40 patients with follicular NHL, and 40 patients with DLBCL will be enrolled at the RP2D to further evaluate safety and efficacy of the combination. Table 3 provides asymptotic 90% confidence intervals for the true probability of response for a range of observed proportions based upon a sample of 40 patients. A sample size of 40 patients is deemed sufficient to provide adequate precision on the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting rate of 45% assuming observed response rates of approximately 60% or higher (~24 responders observed among 40 patients).

Table 3 Potential 90% Interval Estimates for the True Response Probability

Observed Proportion of Responders	*90% Confidence Interval for True Probability of Response*
0.50	*(0.37, 0.63)*
0.60	*(0.47, 0.73)*
0.65	*(0.53, 0.77)*
0.70	*(0.58, 0.82)*
0.75	*(0.64, 0.86)*

Therefore, up to 252 patients may be enrolled in this study.

4.11 DATA QUALITY ASSURANCE

The data will be collected via EDC using eCRFs. The site will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The CRO will be responsible for the data management of this trial, including quality checking of the data.

Genentech will perform oversight of the data management of this trial. Genentech will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central Laboratory data and other electronic data will be sent directly to Genentech, using Genentech's standard procedures to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Genentech and records retention for the study data will be consistent with Genentech's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and physical examinations and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

Genentech or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Genentech or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Genentech or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central Institutional Review Board/ethics committee (IRBs/ECs, except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

5.1.1 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the baseline hematologic malignancy (i.e., leukemia or lymphoma) that were not present prior to the AE reporting period (see Section 5.2.1)

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., medication washout, no treatment run-in, or invasive procedures such as biopsies)
- Preexisting medical conditions other than the disease under study that are judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

5.1.2 Serious Adverse Event

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the investigator (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

5.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions), irrespective of regulatory seriousness criteria. Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.1.6; treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN [of which $\geq$35% is direct bilirubin])
- Suspected transmission of an infectious agent by the study drug
- Grade ≥2 motor neuropathy
- Grade ≥2 infusion reactions

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 5.1) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

5.2.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

After initiation of study drug (the Genentech product(s) or other IMP), all new AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see Section 5.6).

5.2.2 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation timepoints should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.2.3 Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity, and causality.

Table 4 provides guidance for grading AE severity, and Table 5 provides guidance for assessing the causal relationship to the investigational product(s).

The AE grading (severity) scale found in the NCI CTCAE v4.0 will be used for AE reporting.

Table 4 Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Transient or mild discomfort (<48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

AE=adverse event; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; SAE=serious adverse event.

The NCI CTCAE v4.0 can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE (see Section 5.1.2).

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.

To ensure consistency of causality assessments, investigators should apply the following general guidelines:

Table 5 Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

AE=adverse event; SAE=serious adverse event.

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

5.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

5.3.1 Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF. Avoid colloquialisms and abbreviations.

There is one eCRF page for recording AEs or SAEs.

Only one medical concept should be recorded in the event field on the Adverse Event eCRF.

5.3.1.1 Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

5.3.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

5.3.1.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation timepoints. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation timepoints and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF.

5.3.1.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management, e.g., concomitant medication, will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.)

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5 \times$ ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Specific to this study, lymphopenia and leukopenia due to lymphopenia of any grade are expected PD effects of study drug and therefore are not considered to be AEs. However, complications of lymphopenia (e.g., infections) will need to be reported as AEs. In addition, because monocytopenia is not reportable and neutropenia is already being monitored and reported as an AE, leukopenia does not need to be reported as a distinct AE.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

5.3.1.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (including a diagnostic evaluation not mandated in this protocol) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.1.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or a non-serious adverse event of special interest (see Section 5.4.2)

5.3.1.7 Deaths

Deaths that occur during the protocol-specified AE reporting period (see Section 5.2.1) that are attributed by the investigator solely to progression of lymphoma will be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of attribution, will be recorded on the Adverse Event eCRF and expeditiously reported to the Sponsor.

When recording a death on an eCRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Unexplained Death" on the Adverse Event eCRF.

5.3.1.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History eCRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.1.9 Worsening of Baseline Hematologic Malignancy

Worsening and/or progression of the baseline hematologic malignancy (e.g. leukemia or lymphoma) should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

5.3.1.10 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

5.3.1.11 Pregnancy

If a female patient becomes pregnant while receiving the study drug or within 6 months after the last dose of investigational product, a Pregnancy Report eCRF should be completed within 24 hours of learning of the pregnancy. A pregnancy report will automatically be generated and sent to Genentech's Drug Safety Department or its designee. Pregnancy should not be recorded on the Adverse Event eCRF.

Male patients must also be instructed to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study drug. If such an event occurs, it should be reported as described below.

Abortion, whether therapeutic or spontaneous, should always be classified as an SAE (as the Sponsor considers these medically significant), recorded on an Adverse Event eCRF, and expeditiously reported to the Sponsor (see Section 5.4.2).

Any congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and expeditiously reported to the Sponsor (see Section 5.4.2).

After the study period, abortions, congenital anomalies/birth defects, and pregnancy outcomes should still be reported expeditiously to the Sponsor.

In the event the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee within 24 hours of learning of the pregnancy, at the fax numbers listed in Section 5.4.2.

a. Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 1 working day after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee within 24 hours of learning of the pregnancy, at the fax numbers listed in Section 5.4.2.

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

5.4.1 Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an eCRF within 24 hours as described in Section 5.4.2.

Medical Monitor Contact Information for sites in North America:

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Alternate Telephone No.: (888) 835-2555 (U.S. sites only)

For sites outside of North America, local contact details and numbers for safety issues and safety reporting will be provided in the study reference binder.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of SAEs and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to the Sponsor's Safety Risk Management department by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Sites in North America:

Fax No.: [redacted]

Relevant follow-up information should be submitted to Genentech's Drug Safety Department or its designee as soon as it becomes available and/or upon request.

5.5 TYPE AND DURATION OF FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV).

For some SAEs, the Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

5.6 POST-STUDY ADVERSE EVENTS

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt to be related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to Genentech Drug Safety on the study eCRF. If the study eCRF is no longer available, the investigator should report the event directly to Genentech Drug Safety *either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided below.*

Canada:

Fax No.: (905) 542–5864

Email: mississauga.drug_safety@roche.com

United States:

Fax No.: [redacted]

Email: us_drug.safety@gene.com

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with Genentech or a Genentech representative:

- FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

  The names of any subinvestigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae and evidence of licensure of the Principal Investigator and all subinvestigators
- Complete financial disclosure forms for the Principal Investigator and all subinvestigators listed on the FDA Form 1572
- Federalwide Assurance number or IRB statement of compliance
- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)

- A copy of the IRB/EC-approved Informed Consent Form

  Genentech or its designee must review any proposed deviations from the sample Informed Consent Form.
- Current laboratory certification of the laboratory performing the analysis (if other than a Genentech-approved central laboratory), as well as current references ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator Brochure Receipt signed and dated by the Principal Investigator
- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable) , IRB/EC approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator
- Canada only when applicable: original Qualified Investigator Undertaking Form, signed by each Canadian investigator involved in the study
- For global studies, list documents as appropriate for additional countries.

6.2 STUDY COMPLETION

The following data and materials are required by Genentech before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- All laboratory certifications for laboratories performing the analysis (is other than Genentech-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and subinvestigator, FDA Form 1572 for each site)
- A signed and dated Protocol Amendment Acceptance Form(s) [if applicable]
- Updated financial disclosure forms for the Principal Investigator and all subinvestigators listed on the FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

6.3 INFORMED CONSENT FORM

Genentech's Sample Informed Consent Form will be provided to each site. Genentech or its designee must review and approve any proposed deviations from the Sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the Consent Forms during their participation in the study. The final IRB/EC-approved Consent Forms must be provided to Genentech for regulatory purposes.

The Consent Forms must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved Informed Consent Form must be provided to Genentech for regulatory purposes.

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval, and other processes outlined above apply except that IRB/IEC review and approval may not be required per study site policies.

Optional Research Informed Consent

Informed consent for the collection and use of fresh tumor tissue at time of progression for optional research described in Section 4.5.1.10 will be documented in a section of the main Informed Consent Form. This section provides patients with the option to authorize the collection and use of these samples and personal health information for additional research purposes. Agreement to participate in the optional research (by checking the appropriate box in this section of the main Informed Consent Form) is not required for enrollment in the trial but is required prior to any optional research sample collection. Optional consent may be withdrawn at any time by the patient.

6.4 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from Genentech. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's Study File.

6.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Genentech representative to inspect *site facilities and equipment,* study *source* data, patients' medical records, and eCRFs. The Principal Investigator will *oversee all aspects of the conduct of this protocol and* permit Genentech monitors/representatives and collaborators, the FDA, other regulatory agencies, Institutional Review Boards, and the respective national or local health authorities to inspect facilities and records relevant to this study.

6.6 ELECTRONIC CASE REPORT FORMS

eCRFS are to be completed using the [redacted] EDC system. Sites will receive training for appropriate eCRF completion. eCRFs will be submitted electronically to Genentech and should be handled in accordance with instructions from Genentech.

All eCRFs should be completed by designated, trained personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

In addition, at the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

6.7 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing SDV to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where *original* patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, *certified accurate and complete* copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

*Original s*ource documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to *all* applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

6.8 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

In collaboration with the study monitor, Genentech's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

6.9 STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by Genentech. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Genentech with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

6.10 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

6.11 RETENTION OF RECORDS

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of Genentech. Written notification should be provided to Genentech prior to transferring any records to another party or moving them to another location.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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Appendix A-1
Study Flowchart: Initial Study Treatment (*Arms A-B, Cohorts C-D*)

Cycle	Screening	Treatment Period											Treatment Completion/Early Termination Visit [c]	Safety and Survival Follow-Up [d]
		Cycle 1				Cycles 2–4				Cycles 5–17				
Day(s)[a] Assessment	–28 to –1	1 [b]	2	8	15	1 [b]	2	8	15	1 [b]	2	15		
Written informed consent [e]	x													
Review inclusion/exclusion criteria	x													
Medical history and demographics	x													
Height (screening only) and weight	x	x				x				x				
Vital signs	x	x [f]	x [f]	x	x	x [f]	(x) [f]	x	x	x [f]	(x) [f]	x	x	
ECOG Performance Status	x	x		x	x	x		x	x	x			x	
B symptoms [g]	x	x				x				x			x	
Complete physical examination [h]	x													
Targeted physical examination [i]		x	x	x		x	(x)			x	(x)		x	
Concomitant medications	x	x	x	x	x	x	(x)	x	x	x	(x)	x	x	
Adverse events [j]	x	x	x	x	x	x	(x)	x	x	x	(x)	x	x	x
MDASI PRO [k]		Day 1–8 of Cycles 1–8												
12-lead electrocardiogram [l]	x	Refer to Footnote “l”											x	
Tumor assessments [m]	x	Every 3 months											x	
PET scan (required for DLBCL; optional for FL) [m]	x	6-month tumor assessment and as clinically indicated												
Rituximab infusion		x				x				x				
DCDT2980S or DCDS4501A infusion [n]			x			x	(x)			x	(x)			

Appendix A-1 (cont.)
Study Flowchart: Initial Study Treatment (*Arms A-B, Cohorts C-D)*

Cycle	Screening	Treatment Period											Treatment Completion/Early Termination Visit [c]	Safety and Survival Follow-Up [d]
		Cycle 1				Cycles 2–4				Cycles 5–17				
Day(s)[a]														
Assessment	–28 to –1	1 [b]	2	8	15	1 [b]	2	8	15	1 [b]	2	15		
Local Laboratory Assessments														
HBV and HCV screening [o]	x													
Hematology [p]	x	x		x	x	x		x	x	x		x	x	
Serum chemistry [q]	x	x		x	x	x		x	x	x		x	x	
Hemoglobin A1c	x									Cycle 5 Day 1				
Total IgA, IgG, IgM	x									Cycle 8 Day 1			x	
Coagulation (aPTT, PT, and INR)	x													
Pregnancy test [r]	x	Within 10 days of Day 1 of Cycles 3, 6, 9, 12, and 15											x	
Bone marrow biopsy [s]	x	Perform to confirm CR if positive for disease at screening or if clinically indicated												
Central Laboratory Assessments														
Leukocyte immunophenotyping (FACS) [t]		Day 1 of Cycle1, Cycle 4, Cycle 8 and Cycle12											x	
Tumor tissue sample [u]	x												x	
Exploratory plasma (required) and blood (optional) sample [v]	x													
DCDT2980S or DCDS4501A and rituximab pharmacokinetic sampling [w]	Refer to Appendix B-*1 and Appendix B-2*													
Serum sample for anti-DCDT2980S or anti-DCDS4501A antibody [x]														

Appendix A-1 (cont.)
Study Flowchart: Initial Study Treatment (*Arms A-B, Cohorts C-D)*

AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CR = completed response; CT = computed tomography; DLBCL = ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; FL = follicular lymphoma; GGT = γ-glutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; MDASI = MD Anderson Symptom Inventory; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography; PCR = polymerase chain reaction; PT = prothrombin time; QLQ = Quality of Life Questionnaire; SAE = serious adverse event; (x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle —refer to footnote 'n' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 1 year (approximately 17 cycles on an every-21-day schedule) and may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ±1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 3 should occur within ±2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DCDT2980S or DSDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 1 year of total study treatment (approximately 13 cycles).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding rituximab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] Perform within 30 days after the last infusion of DCDT2980S, DCDS4501A, or rituximab. The visit at which response assessment shows progressive disease may be used as the early termination visit. Assessments during the treatment completion/early termination visit may be applied to assessments required to determine eligibility to receive crossover treatment. Patients enrolled into Cohorts C and D are not eligible to receive crossover treatment.

[d] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report from the patient, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-*4* for schedule of assessments during the post-treatment period. Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

[e] Informed consent form(s) must be signed by the patient before any study-specific procedures are performed.

[f] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2 of the protocol.

[g] Defined as unexplained weight loss >10% over previous 6 months, fever (>38°C/100.4°F), and/or drenching night sweats.

[h] Complete physical examination includes all systems described in Section 4.5.1.3.

[i] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDT2980S or DCDS4501A dosing on Day 2 of each cycle if given on separate days from rituximab only if clinically indicated—for example, to follow- up on signs or symptoms observed from the examinations performed on Day 1.

[j] After informed consent is obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs and SAEs, regardless of attribution, must be reported until 30 days following the last administration of study drug or until the patient receives another anti-cancer therapy, whichever occurs first. After this period, investigators should report only SAEs considered related to prior study treatment.

[k] Treatment and disease associated symptoms using the MDASI questionnaire will be collected on hand-held computer devices (see Section 4.5.1.10).

[l] Twelve-lead digital electrocardiogram (ECG) measurements must be obtained in triplicate (with immediately consecutive ECGs obtained until three evaluable ECGs are recorded) at the timepoints specified in Section 4.5.1.5. Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction. The evaluating physician should determine the clinical significance of any abnormal ECGs.

[m] Tumor assessments should be performed at screening and every 3 months while receiving study treatment regardless of study treatment dose schedule. Tumor assessments should also be performed within 30 days after the last study drug infusion as part of the treatment completion/early termination visit. Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C-*1*). For DLBCL patients, a PET scan is required during screening, at the 6-month tumor assessment timepoint and as clinically indicated. For patients with FL, a PET scan is not required but may be obtained based on physician preference and if permitted by local health authorities. Refer to Section 4.5.1.8 for complete details.

[n] Administer DCDT2980S or DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related AEs. For Cycle 1 and Cycle 2, DCDT2980S or DCDS4501A should be administered on the day after rituximab is administered—for example, Day 2 if rituximab is given on Day 1, or Day 3 if rituximab is given as a split dose on Days 1 and 2. In the absence of any infusion-related AEs, rituximab followed by DCDT2980S or DCDS4501A may be administered on the same day in each cycle starting with Cycle 3. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[o] HBsAg, HBcAb, and Hep C Ab serology required. If HBcAb or HCV antibody is positive, HBV/HCV DNA by PCR is required.

[p] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[q] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid. Serum GGT levels will be required at screening only.

[r] A serum pregnancy test should be performed for women of childbearing potential within 14 days prior to receiving first study treatment. In addition, a urine pregnancy test must also be performed within 10 days prior to Day 1 of Cycles 3, 6, 9, 12, and 15, and at the treatment completion/early termination visit unless patient receives crossover treatment, in which case follow the schedule of pregnancy testing outlined in Appendix A-2. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[s] Bone marrow biopsy for morphology (aspirates for morphology and/or flow studies are optional) is required at screening. Bone marrow biopsy for morphology is required at screening and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate

presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated. Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.

[t] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[u] Availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, obtained at any time prior to entry to study. A biopsy of a safely accessible site of disease, defined as requiring only local anesthesia and in general excluding brain, lungs or any internal organs that may subject patients to significant risk, is required for patients who proceed to crossover treatment; if no such lesion exists, then a biopsy is not required.

[v] All patients who have successfully passed screening and are fully eligible for the study will have a 10-mL plasma sample taken for exploratory research.

[w] Pharmacokinetic serum and plasma samples should be drawn according to the schedule provided in Appendices B-1 and B-2.

[x] Whole blood samples for assessment of anti-DCDT2980S or anti-DCDS4501A antibodies in serum will be drawn according to the schedule provided in Appendices B-1 and B-2.

Appendix A-2
Study Flowchart: Crossover Treatment (Patients Randomized to Arms A or B Only)

Cycle	Treatment Period											Crossover Treatment Completion/Early Termination Visit [c]	Safety and Survival Follow-Up [d]
	Cycle 1b				Cycles 2b–4b				Cycles 5b–17b				
Day(s) [a] Assessment	1 [b]	2	8	15	1 [b]	2	8	15	1 [b]	2	15		
Weight	x				x				x				
Vital signs	x [e]	(x) [e]	x	x	x [e]	(x) [e]	x	x	x [e]	(x) [e]	x	x	
ECOG Performance Status	x		x	x	x		x	x	x			x	
B symptoms [f]	x				x				x			x	
Targeted physical examination [g]	x	(x)	x		x	(x)			x	(x)		x	
Concomitant medications	x	(x)	x	x	x	(x)	x	x	x	(x)	x	x	
Adverse events [h]	x	(x)	x	x	x	(x)	x	x	x	(x)	x	x	x
Tumor assessments [i]	Every 3 months											x	
Rituximab infusion	x				x				x				
DCDT2980S or DCDS4501A infusion [j]	x	(x)			x	(x)			x	(x)			
Local Laboratory Assessments													
Hematology [k]	x		x	x	x		x	x	x		x	x	
Serum chemistry [l]	x		x	x	x		x	x	x		x	x	
Total IgA, IgG, IgM									Cycle 8b Day 1			x	
Pregnancy test [m]	Day 1 of Cycles 3b, 6b, 9b, 12b, and 15b											x	
Bone marrow biopsy [n]	Perform to confirm CR if positive for disease at screening or if clinically indicated												
Central Laboratory Assessments													
Leukocyte immunophenotyping (FACS) [o]	Day 1 of Cycle 4, 8, and 12											x	
Tumor biopsy/sample												x [p]	

Appendix A-2 (cont.)
Study Flowchart: Crossover Treatment (Patients Randomized to Arms A or B Only)

AE = adverse event; AL = alanine aminotransferase; AST = aspartate aminotransferase; CR = complete response; LDH = lactate dehydrogenase; SAE = serious adverse event; (x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle—refer to footnote 'j' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 1 year (approximately 17 cycles) and may be given up to ± 2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ± 1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 3 should occur within ± 2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DCDT2980S or DSDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 1 year of total study treatment (approximately 13 cycles).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding rituximab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] Perform within 30 days after the last infusion of DCDT2980S, DCDS4501A or rituximab. The visit at which response assessment shows progressive disease may be used as the early termination visit.

[d] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-4 for schedule of assessments during the post-treatment period. Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

[e] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2 of the protocol.

[f] Defined as unexplained weight loss > 10% over previous 6 months, fever (> 38°C/100.4°F), and/or drenching night sweats.

[g] Targeted physical examinations should be limited to systems of clinical relevance and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDT2980S or DCDS4501A dosing on Day 2 of each cycle if given on separate days from rituximab only if clinically indicated, e.g. to follow -up on signs or symptoms observed from the examinations performed on Day 1.

[h] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-4 for schedule of assessments during the post-treatment period.

[i] Tumor assessments should be performed at screening and every 3 months while receiving study treatment. Tumor assessments should also be

performed 28–56 days after the last study drug infusion as part of the crossover treatment completion/early termination visit. Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C-*1*).

[j] Administer DCDT2980S or DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related adverse events. For Cycle 1b and Cycle 2b, DCDT2980S or DCDS4501A should be administered on the day after rituximab is administered, e.g., Day 2 if rituximab is given on Day 1, or Day 3 if rituximab is given as a split dose on Days 1 and 2. In the absence of any infusion-related adverse events, rituximab followed by DCDT2980S or DCDS4501A may be administered on the same day in subsequent cycles starting with Cycle 3b. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle, but may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[k] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[l] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT), AST, alkaline phosphatase, LDH, and uric acid.

[m] A serum pregnancy test should be performed for women of childbearing potential within 14 days prior to receiving first study treatment. In addition, a serum or urine pregnancy test must be performed within 10 days prior to Day 1 of Cycles 3, 6, 9, 12, and 15 and at the crossover treatment completion/early termination visit. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[n] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[o] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[p] Optional tumor biopsy of a safely accessible site of disease, defined as requiring only local anesthesia and in general excluding brain, lungs or any internal organs that may subject patients to significant risk. Tumor samples will be used for research purposes.

Appendix A-3

Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H): Initial Study Treatment

Cycle	Screening	Treatment Period									Treatment Completion/ Early Termination Visit[c]	End of Treatment Response Assessment (after Cycle 6 Day 1 or last study treatment +6–8 weeks)	Safety and Survival Follow-Up [d]
		Cycle 1				Cycles 2–4		Cycle 4	Cycles 5–8				
Day(s)[a] Assessment	–28 to –1	1[b]	2	8	15	1[b]	2	15[c]	1[b]	2			
Written informed consent[e]	x												
Review inclusion/exclusion criteria	x												
Medical history and demographics	x												
Height (screening only) and weight	x	x				x			x				
Vital signs	x	x[f]	x[f]	x[f]	x[f]	x[f]	(x)[f]		x[f]	(x)[f]	x		
ECOG Performance Status	x	x		x	x	x			x		x		
B symptoms [g]	x	x				x			x		x		
Complete physical examination [h]	x												
Targeted physical examination [i]		x	x	x		x	(x)		x	(x)	x		
Concomitant medications	x	x	x	x	x	x	(x)		x	(x)	x		
Adverse events [j]	x	x	x	x	x	x	(x)		x	(x)	x		x
MDASI PRO [k]		Day 1–8 of Cycles 1–8											
12-lead electrocardiogram[l]	x	Refer to Footnote "l"									x		

Appendix A-3 (cont.)

Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H): Initial Study Treatment

Tumor assessments[m]	x	Every 3 months									x	x	
PET/CT scan (required for DLBCL and FL) [m]	x							x[m]				x [m]	
Obinutuzumab infusion		x		x	x	x			x				
DCDS4501A infusion [n]			x			x	(x)		x	(x)			
Local Laboratory Assessments													
HBV and HCV screening [o]	x												
Hematology [p]	x	x		x	x	x			x		x		
Serum chemistry [q]	x	x		x	x	x			x		x		
Hemoglobin A1c	x								Cycle 5 Day 1				
Total IgA, IgG, IgM	x								Cycle 8 Day 1		x		
Coagulation (aPTT, PT, and INR)	x												
Pregnancy test [r]	x	Within 10 days of Day 1 of Cycles 3, 6									x		
Bone marrow biopsy [s]	x	Perform to confirm CR if positive for disease at screening or if clinically indicated											

Appendix A-3 (cont.)

Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H): Initial Study Treatment

Central Laboratory Assessments													
Leukocyte immunophenotyping (FACS)[t]		Day 1 of Cycle1, Cycle 4, and Cycle 8									x		
Tumor tissue sample [u]	x										x		
Exploratory plasma sample [v]	x												
DCDS4501A and obinutuzumab pharmacokinetic sampling[w]	Refer to Appendix B-3												
Serum sample for anti-DCDS4501A antibody[x]	Refer to Appendix B-3												

Appendix A-3 (cont.)

Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H): Initial Study Treatment

AE = adverse event; ALP = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CR = completed response; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; FLL = follicular lymphoma; GGT = γ-glutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactase dehydrogenase; MDASI = MD Anderson Symptom Inventory; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography; PT = prothrombin time; QLQ = Quality of Life Questionnaire; SAE = serious adverse event; (x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle—refer to footnote 'n' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 6 months (8 cycles on an every-21-day schedule) and may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycle 1 must occur within ±1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 2 should occur within ±2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DSDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 6 months of total study treatment (6 cycles on an every-28-day schedule).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding obinutuzumab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] *Cycle 4 Day 15 assessment should be performed between Cycle 4 Day 15 and Cycle 5 Day 1. The Treatment Completion/Early Termination Visit should be performed* within 30 days after the last infusion of DCDS4501A or obinutuzumab. The visit at which response assessment shows progressive disease may be used as the early termination visit.

[d] Patients will be followed for safety for 30 days after the last infusions of DCDS4501A or obinutuzumab. Such follow-up will require an assessment (per verbal report from the patient, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDS4501A or obinutuzumab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-4 for schedule of assessments during the post-treatment period. Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

[e] Informed consent form(s) must be signed by the patient before any study-specific procedures are performed.

[f] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2 of the protocol.

[g] Defined as unexplained weight loss >10% over previous 6 months, fever (>38°C/100.4°F), and/or drenching night sweats.

[h] Complete physical examination includes all systems described in Section 4.5.1.3.

[i] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDS4501A dosing on Day 2 of each cycle if given on separate days from obinutuzumab only if clinically indicated (e.g., to follow up on signs or symptoms observed from the examinations performed on Day 1).

[j] After informed consent is obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs and SAEs, regardless of attribution, must be reported until 30 days following the last administration of study drug or until the patient receives another anti-cancer therapy, whichever occurs first. After this period, investigators should report only SAEs considered related to prior study treatment.

[k] Treatment and disease associated symptoms using the MDASI questionnaire will be collected on hand-held computer devices (see Section 4.5.1.10). MDASI questionnaire will only be implemented in expansion cohorts (Cohorts G and H).

Appendix A-3 (cont.)

Study Flowchart for Obinutuzumab-Containing Cohorts (E, G-H): Initial Study Treatment

[l] Twelve-lead digital electrocardiogram (ECG) measurements must be obtained in triplicate (with immediately consecutive ECGs obtained until three evaluable ECGs are recorded) at the timepoints specified in Section 4.5.1.5. Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction. The evaluating physician should determine the clinical significance of any abnormal ECGs.

[m] Response should be assessed on the basis of physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C-2). For DLBCL and FL patients, a combined PET/CT scan is required during screening, between Cycle 4 Day 15 and Cycle 5 Day 1, End of Treatment (EOT) assessment, and as clinically indicated. The EOT assessment should be performed 6–8 weeks after Cycle 8 Day 1 or last study treatment. During the follow-up period, refer to Appendix A-5 for imaging assessment during post-treatment follow-up. Refer to Section 4.5.1.8 for complete details for radiographic assessments.

[n] Administer DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related adverse events. For Cycle 1, DCDS4501A should be administered on the day after obinutuzumab is administered (e.g., Day 2 if obinutuzumab is given on Day 1, or Day 3 if obinutuzumab is given as a split dose on Days 1 and 2). In the absence of any infusion-related adverse events, obinutuzumab followed by DCDS4501A may be administered on the same day in each cycle starting with Cycle 2. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle but may be given up to $\pm$2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[o] HBsAg, HBcAb, and Hep C Ab serology required. If HBcAb or HCV antibody is positive, HBV/HCV DNA by PCR is required.

[p] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[q] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid. Serum GGT levels will be required at screening only.

[r] A serum pregnancy test should be performed for women of childbearing potential within 14 days prior to receiving first study treatment. In addition, a urine pregnancy test must also be performed within 10 days prior to Day 1 of Cycles 3, and 6 and at the treatment completion/early termination visit. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[s] Bone marrow biopsy for morphology (aspirates for morphology and/or flow studies are optional) is required at screening and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated. Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.

[t] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[u] Availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, obtained at any time prior to entry to study.

[v] All patients who have successfully passed screening and are fully eligible for the study will have a 10-mL plasma sample taken for exploratory research prior to receiving study treatment.

[w] Pharmacokinetic serum and plasma samples *and pharmacodynamics blood samples* should be drawn according to the schedule provided in Appendix B-3.

[x] Whole blood samples for assessment of anti-DCDS4501A or anti-obinutuzumab antibodies in serum will be drawn according to the schedule provided in Appendix B-3.

Appendix A-4
Study Flowchart: Post-Treatment Follow-Up *for Rituximab-Containing Regimens (Arms A-B, Cohorts C-D)*

Assessments/Procedures	Post-treatment Follow-up				
Months after treatment completion visit	2 Months	4 Months	6 Months	9 Months	12 Months
Targeted physical examination [a]	x	x	x	x	x
Vital signs (blood pressure, pulse rate, and body temperature)	x	x	x	x	x
ECOG Performance Status	x	x	x	x	x
B symptoms [b]	x	x	x	x	x
Tumor assessments [c]	x	x	x	x	x
Total IgA, IgG, IgM	x	x	x	x	x
Hematology [d]	x	x	x	x	x
Serum chemistry [e]	x	x	x	x	x
Bone marrow [f]	Perform to confirm CR if positive for disease at screening or if clinically indicated				
Central Lab Assessments					
Leukocyte immunophenotyping (FACS) [g]	x	x	x	x	x
Pharmacokinetic sampling [h]	x	x	x		
Serum sample for anti-DCDT2980S / anti-DCDS4501A ATA assay [h]	x	x	x		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATA = anti-therapeutic antibody; CR = completed response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; Ig = immunoglobulin; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography.

NOTE: Post-treatment assessments apply to patients who discontinue from study treatment (initial or crossover

treatment) for reasons other than disease progression. The schedule corresponds to visits timed from treatment completion/early termination visit or crossover treatment completion/early termination visit until the time of disease progression, start of new anti-cancer therapy, or withdrawal from study participation. Two-month and 4-month follow-up visits should occur within ±7 days from the scheduled date, while subsequent visits should occur within ±14 days from the scheduled date.

[a] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms.

[b] Defined as unexplained weight loss >10% over previous 6 months, fever (>38°C/100.4°F), and/or drenching night sweats.

[c] Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C).

[d] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[e] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), and uric acid.

[f] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[g] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[h] Refer to Appendices B-1 or B-2.

Appendix A-5

Study Flowchart: Post-Treatment Follow-Up for Obinutuzumab-Containing Regimens (Cohorts E, G-H)

Assessments/Procedures	Post-Treatment Follow-Up					
Months after treatment completion visit	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Targeted physical examination [a]	x	x	x	x	x	x
Vital signs (blood pressure, pulse rate, and body temperature)	x	x	x	x	x	x
ECOG Performance Status	x	x	x	x	x	x
B symptoms [b]	x	x	x	x	x	x
Tumor assessments [c]	x	x	x	x	x	x
Total IgA, IgG, IgM	x	x	x	x	x	x
Hematology [d]	x	x	x	x	x	x
Serum chemistry [e]	x	x	x	x	x	x
Bone marrow [f]	Perform to confirm CR if positive for disease at screening or if clinically indicated					
Central Lab Assessments						
Leukocyte immunophenotyping (FACS) [g]	x	x	x	x	x	x
Pharmacokinetic sampling [h]	x	x				
Serum sample for anti-DCDT2980S/anti-DCDS4501A, anti-obinutuzumab ATA assay [h]	x	x		x [h]		x [h]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATA = anti-therapeutic antibody; CR = completed response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorting; Ig = immunoglobulin; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography.

Appendix A-5 (cont.)
Study Flowchart: Post-Treatment Follow-Up *for Obinutuzumab-Containing Regimens (Cohorts E, G-H)*

NOTE: Post-treatment assessments apply to patients who discontinue from study treatment (initial or crossover treatment) for reasons other than disease progression. The schedule corresponds to visits timed from treatment completion/early termination visit or crossover treatment completion/early termination visit until the time of disease progression, start of new anti-cancer therapy, or withdrawal from study participation. Two-month and four-month follow-up visits should occur within ±7 days from the scheduled date, while subsequent visits should occur within ±14 days from the scheduled date.

[a] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms.

[b] Defined as unexplained weight loss >10% over previous 6 months, fever (>38°C/100.4°F), and/or drenching night sweats.

[c] Response should be assessed on the basis of physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C-2). CT or combined PET/CT scan should be obtained during the post-treatment follow-up.

[d] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[e] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid.

[f] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[g] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[h] Refer to Appendix B-3.

Appendix B-1
Serum and Plasma Pharmacokinetic Schedule for DCDT2980S/DCDS4501A and Rituximab, and ATA Schedule for DCDT2980S/DCDS4501A (For Patients Receiving Rituximab on Day 1 and DCDT2980S/DCDS4501A on Day 2 of Every Cycle)
(Arms A-B, Cohorts C-D)

Study Visit	Sample Timepoint(s) [a]	Samples [b]
Cycle 1, Day 1	Pre-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycle 1, Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • DCDT2980S/DCDS4501A PK [b]
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 1, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 1, Day 15 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycles 2–3, Day 1	Pre-rituximab dose	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycles 2–3, Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 3, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 3, Day 15 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycles 4, and every 4th cycle thereafter), Day 1	Pre-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycles 4, and every 4th cycle thereafter), Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (± 15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK

Appendix B-1 (cont.)
Serum and Plasma Pharmacokinetic Schedule for DCDT2980S/DCDS4501A and Rituximab, and ATA Schedule for DCDT2980S/DCDS4501A (For Patients Receiving Rituximab on Day 1 and DCDT2980S/DCDS4501A on Day 2 of Every Cycle)
(Arms A-B, Cohorts C-D)

Study Visit	Sample Timepoint(s) [a]	Samples [b]
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK [e]
Post-treatment Follow-Up Visits [d]	2, 4, and 6 months after treatment completion visit	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Note: "Pre-infusion" means prior to the start of infusion; "Post-infusion" means after the infusion is completed.

[a] A 3-mL whole-blood sample will be taken for each of the following at each specified timepoint: anti-DCDT2980S or anti-DCDS4501A antibody; rituximab PK; and/or DCDT2980S/DCDS4501A PK. If rituximab dosing is split over two days, then PK will be obtained prior to the rituximab dose on the first day and 30 minutes (±15 minutes) post-rituximab infusion on the second day.

[b] PK sampling will not be obtained from patients who cross-over to another treatment arm.

[c] Cycles 2 and 4 only for anti-DCDT2980S or anti-DCDS4501A antibody.

[d] Post-treatment follow-up PK and ATA assessments only apply to patients who did not receive crossover treatment.

[e] DCDT2980S/DCDS4501A PK including serum PK samples for total DCDT2980S and DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

Appendix B-2
Serum and Plasma Pharmacokinetic Schedule for Rituximab and DCDT2980S/DCDS4501A, and ATA Schedule for DCDT2980S/DCDS4501A for Patients Receiving Rituximab and DCDT29808S/DCDS4501A on Day 1 of Every Cycle Beginning Cycle 3 *(Arms A-B, Cohorts C-D)*

Study Visit	Sample Timepoint(s) [a]	Samples [b]
For Cycle 1 and Cycle 2 PK assessments, refer to Appendix B-1		
Cycle 3, Day 1	Pre-rituximab infusion	• Rituximab PK • DCDT2980S/DCDS4501A PK [e]
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 3, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 3, Day 15 (±1 day)		• Rituximab • DCDT2980S/DCDS4501A PK
Cycles 4, and every 4th cycle thereafter), Day 1	Pre-rituximab infusion	• Rituximab PK • Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK
Post-treatment Follow-Up Visits [d]	2, 4, and 6 months after treatment completion visit	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK

Appendix B-2 (cont.)
Serum and Plasma Pharmacokinetic Schedule for Rituximab and DCDT2980S/DCDS4501A, and ATA Schedule for DCDT2980S/DCDS4501A for Patients Receiving Rituximab and DCDT29808S/DCDS4501A on Day 1 of Every Cycle Beginning Cycle 3 *(Arms A-B, Cohorts C-D)*

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Note: "Pre-infusion" means prior to the start of infusion; "Post-infusion" means after the infusion is completed.

[a] A 3-mL whole-blood sample will be taken for each of the following at each specified timepoint: anti-DCDT2980S or anti-DCDS4501A antibody, rituximab PK, and/or DCDT2980S/DCDS4501A PK. If rituximab dosing is split over two days, then PK will be obtained prior to the rituximab dose on the first day and 30 minutes (±15 minutes) post-rituximab infusion on the second day.

[b] PK sampling will not be obtained from patients who cross-over to another treatment arm.

[c] Cycles 4 only for anti-DCDT2980S or anti-DCDS4501A antibody.

[d] Post-treatment follow-up PK and ATA assessments only apply to patients who did not receive crossover treatment.

[e] DCDT2980S/DCDS4501A PK including serum PK samples for total DCDT2980S and DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

Appendix B-3
Serum and Plasma Pharmacokinetic, Blood Pharmacodynamic, and ATA Schedule for Obinutuzumab and DCDS4501A (Cohorts E, G-H)

Study Visit	Sample Timepoint(s) [a]	Samples [a]
Cycle 1, Day 1	Pre-obinutuzumab infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • *PD Blood* [c]
	End of obinutuzumab infusion	• Obinutuzumab PK (serum) • *PD Blood* [c]
Cycle 1, Day 2	Pre-DCDS4501A infusion	• DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • *PD Blood* [c]
	End of DCDS4501A infusion	• DCDS4501A PK (serum and plasma)[b] • *PD Blood* [c]
Cycle 1, Day 8	6 days (±1 day) after Day 2 infusion	• DCDS4501A PK (serum and plasma)[b] • *PD Blood* [c]
Cycle 1, Day 15	13 days (±1 day) after Day 2 infusion	• DCDS4501A PK (serum and plasma)[b] • *PD Blood* [c]
Cycle 2, Day 1	Pre-obinutuzumab infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • *PD Blood* [c]
	End of obinutuzumab infusion	• *PD Blood*[c]
	Pre-DCDS4501A infusion	• DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • *PD Blood* [c]
	End of DCDS4501A infusion	• *PD Blood*
Cycle 4, Day 1	Pre-obinutuzumab infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum)
	End of obinutuzumab infusion	• Obinutuzumab PK (serum)
	Pre-DCDS4501A infusion	• DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b]
	End of DCDS4501A infusion	• DCDS4501A PK (serum and plasma)[b]
Cycle 4 Day 15	*Aligned with PET imaging*	• *PD Blood* [c]
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b]
End of Treatment Assessment Visit	6–8 weeks after last study dose	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • *PD Blood* [c]

Appendix B-3 (cont.)

Serum and Plasma Pharmacokinetic and ATA Schedule for Obinutuzumab and DCDS4501A ***(Cohorts E, G-H)***

Post-treatment Follow-Up Visits	*3* and 6 months after treatment completion visit	• Obinutuzumab ATA (serum) • Obinutuzumab PK (serum) • DCDS4501A ATA (serum) • DCDS4501A PK (serum and plasma)[b] • *PD Blood* [c]
	9 months after treatment completion visit	• *PD Blood* [c]
	12 and 18 months after treatment completion visit	• *Obinutuzumab ATA (serum)* • *Obinutuzumab PK (serum)* • *PD Blood* [c]
	24 months after treatment completion visit	• *PD Blood* [c]

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

Note: "Pre-infusion" means prior to the start of infusion; "End-of-infusion" samples should be drawn 30 minutes (±15 minutes) unless otherwise specified.

[a] Up to 10-mL whole-blood samples will be taken for obinutuzumab PK, obinutuzumab ATA, obinutuzumab concentration, DCDS4501A PK (DCDS4501A total antibody, unconjugated MMAE and conjugate [evaluated as antibody-conjugated MMAE]), DCDS4501A ATA, DCDS4501A concentration, and for exploratory studies at each specified point with separate tubes for plasma or serum samples. If obinutuzumab dosing is split over two days, then PK will be obtained prior to the obinutuzumab dose on the first day and 30 minutes (±15 minutes) post-obinutuzumab infusion on the second day.

[b] DCDS4501A PK including serum PK samples for total DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

[c] *Up to 10-mL whole-blood samples will be taken for exploratory studies at each specified timepoint with separate tubes.*

Appendix C-*1*
Modified Response and Progression Criteria for NHL

Adapted from: Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol 2007;25:579–86.

Selection of Indicator (Target) Lesions

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions

  Abnormal lymph nodes are those that are either

  > 15 mm in the greatest transverse diameter (GTD) regardless of the short axis diameter, or

  > 10 mm in short axis diameter regardless of long axis

- If possible, they should be from disparate regions of the body.
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

PET Scans--Definition of a Positive PET scan

Visual assessment currently is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary. In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff. Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen uptake, and diffusely increased bone marrow uptake within weeks after treatment.

Complete Remission (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy.

   Typically FDG-avid lymphoma: in patients with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

   Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, the designation

of CR requires all nodal indicator lesions to regress to the size of normal lymph nodes. Lymph nodes that were >15 mm in GTD regardless of the short axis diameter at the screening tumor assessment must regress to ≤ 15 mm in GTD regardless of the short axis diameter. Lymph nodes that were 11 to 15 mm in GTD and >10 mm in the short axis diameter at the screening tumor assessment must regress to ≤ 10 mm in the short axis diameter.

2. The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

3. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (>20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial Remission (PR)

1. $\geq 50\%$ decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; (b) if possible they should be from disparate regions of the body; (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by $\geq 50\%$ in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

6. No new sites of disease should be observed (e.g., nodes >1.5 cm in any axis).

7. *Typically FDG-avid lymphoma*: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. *Variably FDG-avid lymphomas/FDG-avidity unknown*: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

1. In patients with follicular lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease (SD)

1. Failing to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease (see below).

2. *Typically FDG-avid lymphomas*: the PET should be positive at prior sites of disease with no new areas of involvement on the post- treatment CT or PET.

3. *Variably FDG-avid lymphomas/FDG-avidity unknown*: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (RD; after CR) or Progressive Disease (PD; for Patients with PR or SD)

1. Lymph nodes should be considered abnormal if the long axis is $>$ 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1–1.5 cm, it should only be considered abnormal if its short axis is $>$ 1.0. Lymph nodes $\leq$ 1.0 cm by $\leq$ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

2. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities.

3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq$ 50% and to a size of 1.5 $\times$ 1.5 cm or more than 1.5 cm in the long axis.

4. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

5. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 15 mm in its long axis by CT).

6. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease.

Appendix C-2
Revised Criteria for Response Assessment: The Lugano Classification (Cohort E, G-H)

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol. 2014 Aug [cited 2014 Aug 29]. Available from: http://jco.ascopubs.org/content/early/2014/08/11/JCO.2013.54.8800.long.

Selection of measured dominant (indicator) lesions:

- Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters

  A measurable node must have an LDi greater than 1.5 cm.

  A measurable extranodal lesion should have an LDi greater than 1.0 cm.
- Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.
- Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation.
- If possible, they should be from disparate regions of the body.
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

Selection of non-measured (non-indicator) lesions:

- Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured.

  These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

Appendix C-2 (cont.)

Revised Criteria for Response Assessment: The Lugano Classification (Cohort E, G-H)

In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, and bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

Response	Site	PET-CT–based Response	CT-based Response
Complete		**Complete metabolic response**	**Complete radiologic response (all of the following)**
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS** It is recognizes that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to $\leq$ 1.5 cm in LDi No extralymphatic sites of disease
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial		**Partial metabolic response**	**Partial remission (all of the following)**
	Lymph nodes and extralymphatic sites	Score of 4 or 5** with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	$\geq$ 50% decrease in SPD of up to 6 target measureable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm $\times$ 5 mm as the default value When no longer visible, 0 $\times$ 0 mm For a node $>$ 5 mm $\times$ 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by $>$ 50% in length beyond

Appendix C-2 (cont.)

Revised Criteria for Response Assessment: The Lugano Classification (Cohort E, G-H)

Response	Site	PET-CT–based Response	CT-based Response
			normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease		**No metabolic response**	**Stable disease**
	Target nodes/nodal masses, extranodal lesions	Score 4 or 5** with no significant change in FDG uptake from baseline at interim or end of treatment	$<$50% decrease from baseline in SPD for up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Nonmeasured lesions	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease		**Progressive metabolic disease**	**Progressive disease (requires at least 1 of the following)**
	Individual target nodes/nodal lesions	Score 4 or 5** with an increase in intensity of uptake from baseline and/or	PPD progression: An individual node/lesion must be abnormal with: • LDi $>$1.5 cm AND • Increase by $\geq$50% from PPD nadir AND An increase in LDi or SDi from nadir • 0.5 cm for lesions $\leq$2 cm • 1.0 cm for lesions $>$2 cms
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	
	Nonmeasured lesions	None	New or clear progression of preexisting

Appendix C-2 (cont.)

Revised Criteria for Response Assessment: The Lugano Classification (Cohort E, G-H)

Response	Site	PET-CT–based Response	CT-based Response
	Organ enlargement		In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-acid foci	New or recurrent involvement

5-PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

**PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake < mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Appendix D
Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Appropriate monitors (electrocardiogram, blood pressure, pulse oximetry
- Oxygen
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines.
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional assistance!
- Maintain an adequate airway.
- *Provide oxygen as needed.*
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible.
- Administer antihistamines, epinephrine, *inhaled bronchodilators,* or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix E
M. D. Anderson Symptom Inventory (MDASI)

M.D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24*** hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (symptom is as bad as you can imagine it could be) for each item.

	Not Present										**As Bad As You Can Imagine**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problems **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problems with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your **mouth/throat sores** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **diarrhea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your problems with **weakness in the arms or legs** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Appendix E (cont.)
M. D. Anderson Symptom Inventory (MDASI)

Part II. How have your symptoms interfered with your life?
Symptoms frequently interfere with how you feel and function. How much have your symptoms interfered with the following items **in the last 24** hours:

	Did Not Interfere										**Interfered Completely**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
18. General activity?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
19. Mood?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
20. Work (including work around the house)?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
21. Relations with other people?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
22. Walking?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
23. Enjoyment of life?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Appendix F
Recommendations for the Use of White Blood Cell Growth Factors

Primary Prophylactic G-CSF Administration (First and Subsequent-Cycle Use)

Primary prophylaxis with G-CSF is recommended if any of the following clinical factors are present:

- Age >65 years
- Poor performance status
- Previous history of febrile neutropenia
- Open wounds or active infections
- More advanced cancer
- Extensive prior treatment, including large radiation therapy ports
- Cytopenias due to bone marrow involvement by tumor
- Other serious comorbidities

Secondary Prophylactic G-CSF Administration

Prophylactic G-CSF administration is recommended for patients who fulfill each of the following circumstances:

- Experienced a neutropenic complication from a prior cycle of study treatment
- Primary prophylactic G-CSF was not received; and
- The intent is to avoid dose reduction of the antibody–drug conjugate (ADC), where the effect of the reduced dose on disease-free, overall survival or treatment outcome is not known

Therapeutic Use of G-CSF

G-CSF administration should be considered for the following patients:

- Patients with febrile neutropenia who are at high risk for infection-associated complications; or
- Patients who have prognostic factors that are predictive of poor clinical outcome, e.g., prolonged (>10 days) and profound (<100/μL) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of fever development

Source: Smith TJ et al. 2006 Update of Recommendations for the use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. JCO 24:3187-3205. 2006.

PROTOCOL

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF DCDT2980S IN COMBINATION WITH RITUXIMAB OR DCDS4501A IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
EUDRACT NUMBER:	2011-004377-84
STUDY DRUG:	DCDT2980S; DCDS4501A
IND:	107713
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	27 July 2012
DATE AMENDED:	Version 1: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	24-Jun-2013 17:51:55

PROTOCOL AMENDMENT SUMMARY:
VERSION 1

RATIONALE

Protocol GO27834 has been amended to enable the following changes:

- Additional cohorts of approximately 20 patients each (denoted Cohort C and Cohort D) to assess DCDT2980S and DCDS4501A at a dose of 1.8 mg/kg in combination with rituximab at a dose of 375 mg/m^2 in patients with relapsed/refractory follicular lymphoma have been added. The purpose of enrolling additional cohorts of patients with follicular lymphoma is to determine whether the lower dose level of antibody–drug conjugate (ADC) in combination with standard doses of rituximab result in improved tolerability while maintaining efficacy in follicular lymphoma. The opening of either or both cohorts will be at the Sponsor's discretion based on safety and clinical activity observed in the randomized part of the study. Patients will not be randomized to one cohort or another. Only select investigator sites that have agreed to participate in this nonrandomized portion of the study will enroll patients into these cohorts.
- Patients enrolled into Cohorts C and D will not be eligible to receive crossover treatment. Cohorts C and D will support the study's primary objectives to assess safety, tolerability, and anti-tumor activity of the ADCs (plus rituximab) at the 1.8-mg/kg dose level.
- Updated safety and efficacy information from the ongoing Phase I studies (DCT4862g and DCS4968g) have been provided (see Sections 1.2.1 and 1.2.2).
- The definitions of progression free survival (PFS) and overall survival have been updated (see Section 4.10.4).
- Procedures for reporting non-serious adverse events of special interest and serious adverse events have been updated (see Sections 5.1.3 and 5.4).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

SUMMARY OF CHANGES:
VERSION 1

PROTOCOL AMENDMENT ACCEPTANCE FORM

A Protocol Amendment Acceptance Form has been added.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2.1.2: DCDT2980S Clinical Data

a. Patient Enrollment

All data presented herein is based on a data entry cutoff of *22 February 2013*~~22 June 2012~~, *with clinical data available* from *65*~~49~~ patients with NHL *(excluding patients with CLL)* enrolled in dose-escalation and expansion cohorts. These include ~~36~~*49* patients who were treated with single-agent DCDT2980S at doses ranging from 0.1 to 3.2 mg/kg administered intravenously every 21 days, and ~~13~~*16* patients who were enrolled into two Phase Ib cohorts with DCDT2980S administered at doses of 1.8 mg/kg (5 patients) and 2.4 mg/kg (~~8~~*11* patients) in combination with 375 mg/m^2 rituximab.

~~Seven patients have been enrolled~~ *Enrollment* into CLL dose escalation cohorts *was closed on 31 May 2013*~~to date~~. Refer to the DCDT2980S Investigator Brochure for details regarding clinical data in CLL patients.

b. Pharmacokinetics

Preliminary pharmacokinetic analysis based on available data *as of 22 June 2012* is summarized below.

c. Safety

Dose Limiting Toxicity

Separate dose-escalation cohorts enrolled patients with B-cell NHL and CLL. For the NHL dose escalation, DLTs of Grade 4 neutropenia occurred in 1 patient out of 3 DLT-evaluable patients in the 3.2 mg/kg single agent cohort and 1 patient out of ~~8~~ *11* DLT-evaluable patients in the 2.4 mg/kg + rituximab cohort. Consequently, DCDT2980S at 2.4 mg/kg was determined to be the recommended Phase II dose (RP2D) as both monotherapy and in combination with rituximab. ~~Patients are currently being enrolled in monotherapy expansion cohorts for various types of NHL in order to collect and further characterize both single agent and combination safety data.~~

For the CLL dose-escalation cohorts, one DLT ~~out of six DLT evaluable patients~~ was reported *to date*…

Single-Agent DCDT2980S ***and DCDT2980S Combined with Rituximab in NHL***

Enrollment into NHL indication-specific monotherapy expansion cohorts and the DCDT2980S plus rituximab cohorts has been completed.

Forty-nine patients received single-agent DCDT2980S at a starting dose of ≥ 1.8 mg/kg (7 at 1.8 mg/kg, 42 at 2.4 mg/kg); 16 patients received DCDT2980S at a starting dose of ≥ 1.8 mg/kg in combination with rituximab (5 at 1.8 mg/kg, 11 at 2.4 mg/kg). Overall the safety profile of DCDT2980S combined with rituximab did not differ from that of single-agent DCDT2980S.

Treatment emergent hematologic and commonly reported nonhematologic adverse events for all grades in patients treated with single-agent DCDT2980S and DCDT2980S plus rituximab included neutropenia (29%), febrile neutropenia (3%), infection (system organ class; 43%), anemia (25%), thrombocytopenia (12%), peripheral neuropathy (28%), diarrhea (40%), pyrexia (14%), nausea (34%), and fatigue (55%). Treatment emergent Grade ≥ 3 adverse events included neutropenia (25%), febrile neutropenia (3%), infection (system organ class; 11%), anemia (5%), peripheral neuropathy (3%), diarrhea (5%), pyrexia (2%), and fatigue (3%). Serious adverse events assessed by the treating investigator to be related to DCDT2980S were reported in 21% of patients. Dose discontinuations for adverse events were reported in 20% of patients.

Refer to the DCDT2980S Investigator's Brochure for complete and updated details related to safety. ~~Adverse events regardless of relationship to study drug were reported in 32 of 36 NHL patients (97.0%) enrolled into the single-agent dose cohorts.~~

~~The most common of these adverse events in ≥ 10% of patients were neutropenia (7 patients 21.2%), anaemia (7 patients 21.2%), nausea (10 patients 30.3%), diarrhea (11 patients 33.3%), constipation (7 patients 21.2%), vomiting (7 patients 21.2%), abdominal pain (8 patients 24.2%), fatigue (11 patients 33.3%), peripheral oedema (7 patients 21.2%), pyrexia (6 patients 18.2%), chest discomfort (4 patients 12.1%), upper respiratory tract infection (5 patients 15.2%), decreased appetite (8 patients 24.2%), pain (10 patients 30.3%), dizziness (6 patients 18.2%), cough (6 patients 18.2%), dyspnea (6 patients 18.2%), nasal congestion (4 patients 12.1%), rash (5 patients 15.2%) and neuropathy (5 patients 15.2%).~~

~~All patients treated at the RP2D of 2.4 mg/kg (n = 10 enrolled in dose escalation and expansion cohorts) experienced an adverse event. The most common adverse events of all grades in ≥ 2 patients were anaemia (3 patients), nausea (3 patients), fatigue (3 patients), dizziness (3 patients), vomiting (2 patients), constipation (2 patients), chills (2 patients), decreased appetite (2 patients), dyspnea (2 patients), alopecia (2 patients), and peripheral neuropathy (2 patients).~~

Grade ≥3 adverse events regardless of relationship to study drug were reported in 21 (58.3%) of 36 NHL patients enrolled into the single-agent dose cohorts. Neutropenia was reported in 8 (24.2%) patients. Grade 3–5 adverse events reported in ≥ 2 patients included hyperglycemia (3 patients), anemia (3 patients), diarrhea, hyponatremia, hypoxia, pneumonia, peripheral neuropathy, and dehydration (2 patients each).

Six patients treated at the RP2D of 2.4 mg/kg (n = 10 enrolled in dose-escalation and expansion cohorts) experienced a Grade 3–5 adverse event. Grade 3–4 neutropenia was reported in 2 patients. No other Grade 3–5 adverse event was reported in more than 1 patient.

Across all treatment cohorts a total of 24 serious adverse events have been reported in 14 patients (25.0%). Three of these serious adverse events occurring in 3 patients (12.5%) were considered related to study drug treatment. These included the Grade 5 febrile neutropenia in a CLL patient treated with one cycle of DCDT2980S at 1.0 mg/kg (described in the previous section), a Grade 3 pneumonia in a CLL patient treated one cycle of DCDT2980S at 1.8 mg/kg, and a Grade 3 dehydration in a NHL patient enrolled in the 3.2 mg/kg single-agent DCDT2980S dose-escalation cohort.

No serious adverse events were reported among patients treated at the RP2D of 2.4 mg/kg single-agent DCDT2980S.

DCDT2980S in Combination with Rituximab

DCDT2980S in combination with rituximab was administered in two dose cohorts of 1.8 mg/kg and 2.4 mg/kg. Adverse events regardless of relationship to study drug were reported in 9 patients receiving rituximab in combination with DCDT2980S. The most common of these adverse events in ≥ 2 patients were nausea (3 patients), fatigue (3 patients), and rash (3 patients).

Four of 8 patients treated at the RP2D of 2.4 mg/kg of DCDT2980S experienced an adverse event. Adverse events occurring in 2 or more patients included nausea and decreased appetite.

Grade ≥3 adverse events regardless of relationship to study drug were reported in 6 (46.2%) of patients taking rituximab in combination with DCDT2980S. The most common event occurring in 2 or more patients was neutropenia, with 1 patient in each of the two combination therapy cohorts (1.8 mg/kg and 2.4 mg/kg of DCDT2980S) reporting Grade 3–5 neutropenia. No other Grade 3-5 adverse event was reported in more than 1 patient.

One serious adverse event of shortness of breath unrelated to DCDT2980S was reported in a patient treated with 2.4 mg/kg DCDT2980S in combination with rituximab.

d. ~~Preliminary~~ Efficacy *in Non-Hodgkin's Lymphoma*

Investigator-based objective responses were observed in 17 of 43 (40%) patients treated with single-agent DCDT2980S and 5 of 15 (33%) patients treated with DCDT2980S combined with rituximab. Among patients with relapsed/refractory DLBCL, 11 of 28 (39%) objective responses (5 complete responses [CR] and 6 partial responses [PR]) were observed with single-agent DCDT2980S and 3 of 7 (43%; 2 CR, 1 PR) with DCDT2980S combined with rituximab. Among patients with relapsed/refractory indolent (iNHL), 6 of 13 (46%) objective responses (2 CR, 4 PR) were observed with single-agent DCDT2980S and 1 of 4 (PR) with DCDT2980S combined with rituximab.
~~To date, no formal analysis of anti tumor activity has been performed for Study DCT4862g. Anti tumor activity has been reported in patients treated with single agent DCDT2980S as well as DCDT2980S when combined with rituximab.~~

Refer to the DCDT2980S Investigator Brochure for complete and updated details *related to* ~~regarding~~ anti-tumor activity.

SECTION 1.2.2.2: DCDS4501A Clinical Data

a. Patient Enrollment

All data presented herein is based on a data entry cutoff of *28 February 2013*~~22 June 2012~~, with clinical data available from *60*~~39~~ patients with NHL *(excluding patients with CLL)* enrolled in dose-escalation and expansion cohorts. These include *51*~~32~~ patients who were treated with single-agent DCDS4501A ranging from 0.1 to 2.4 mg/kg administered intravenously every 21 days, and *9*~~7~~ patients who were enrolled into a single Phase Ib cohort with DCDS4501A administered at a dose of 2.4 mg/kg ~~(8 patients)~~ in combination with 375 mg/m^2 rituximab.

~~Ten patients have been enrolled into CLL dose escalation cohorts to date.~~ *In the CLL dose escalation cohorts, two DLTs were reported at the single-agent dose of 1.8 mg/kg. Enrollment into the CLL cohorts was stopped on 7 January 2013.* Refer to the DCDS4501A Investigator Brochure for details regarding clinical data in CLL patients.

b. Pharmacokinetics

Preliminary pharmacokinetic analysis based on available data *as of 22 June 2012* is summarized below…

c. Safety

Dose-Limiting Toxicities

DLT of Grade 4 neutropenia occurred in 1 patient out of 10 DLT-evaluable patients in the 2.4 mg/kg single agent cohort and 1 patient out of ~~7~~ *9* DLT-evaluable patients in the 2.4 mg/kg + rituximab cohort…

In the CLL dose-escalation cohorts, two DLTs were reported at the single-agent dose of 1.8 mg/kg. One patient had a Grade 4 neutropenia, and 1 patient had a Grade 4 invasive fungal infection.

Single-Agent DCDS4501A ***and DCDS4501A Combined with Rituximab***

Fifty-one patients received single agent DCDS4501A at a starting dose of ≥ 1.8 mg/kg (6 at 1.8 mg/kg, 45 at 2.4 mg/kg); an additional 9 patients received DCDS4501A at a dose of 2.4 mg/kg in combination with rituximab. Overall, the safety profile of DCDS4501A combined with rituximab did not differ from that of single-agent DCDS4501A.

Treatment emergent hematologic and commonly reported non-hematologic adverse events for all grades in patients treated with single-agent DCDS4501A and DCDS4501A plus rituximab included neutropenia (50%), febrile neutropenia (5%), infection (system organ class; 35%), anemia (13%), thrombocytopenia (18%), peripheral neuropathy (32%), diarrhea (43%), pyrexia (37%), nausea (35%), and fatigue (18%). Treatment emergent Grade ≥ 3 adverse events included neutropenia (43%), febrile neutropenia (5%), infection (system organ class; 10%), anemia (8%), peripheral neuropathy (7%), diarrhea (3%), pyrexia (2%), and fatigue (5%). Serious adverse events assessed by the treating investigator to be related to DCDS4501A were reported in 20% of patients. Dose discontinuations for adverse events were reported in 33% of patients.

Refer to the DCDS4501A Investigator's Brochure for complete and updated details related to safety.

~~Adverse events regardless of relationship to study drug were reported in 31 (96.9%) NHL patients enrolled into the single agent dose- escalation cohorts. Across all dose-escalation cohorts, the most common adverse events in ≥ 10% of treated patients were neutropenia/febrile neutropenia (17 patients- 53.1%), anaemia (6 patients- 18.8%), leukopenia (9 patients- 28.1%), thrombocytopenia (6 patients- 18.8%), nausea (10 patients- 31.2%), diarrhea (9 patients- 28.1%), constipation (9 patients- 28.1%), vomiting (5 patients- 15.6%), pyrexia (11 patients- 34.4%), fatigue (10 patients- 31.2%), chills (8 patients- 25.0%), peripheral oedema (4 patients- 12.5%), hyperglycaemia (10 patients- 31.2%), decreased appetite (5 patients- 15.6%), dizziness (4 patients- 12.5%), dysgeusia (4 patients- 12.5%), peripheral neuropathy (6 patients- 18.8%), cough (8 patients- 25.0%) and dyspnoea (5 patients- 15.6%).~~

~~Eleven of twelve patients treated at the RP2D of 2.4 mg/kg (91.7%) experienced an adverse event. The most common adverse events of all Grades in ≥ 2 patients were neutropenia (unmapped term, 4 patients), neutropenia (mapped term, 3 patients), diarrhea (3 patients), anemia, nausea, pyrexia, alopecia, thrombocytopenia (unmapped~~

term), leukopenia (unmapped term), hypokalemia (unmapped term), and hyperglycemia (unmapped term).

Grade ≥ 3 adverse events regardless of relationship to study drug were reported in 22 (68.8%) of NHL patients treated with single agent DCDS4501A across all dose levels. The most common of these events in ≥ 10% of patients were neutropenia (13 patients 40.6%) and leukopenia (5 patients 15.6%).

Seven of twelve patients treated at the RP2D of 2.4 mg/kg experienced a Grade 3 5 adverse event. Grade 3 4 events in reported in 2 or more patients included neutropenia (unmapped term, 4 patients), neutropenia (mapped term), leukopenia (unmapped term), and anemia, (2 patients each).

A total of 27 serious adverse events were reported in 15 patients (30.6%) across all dose levels. Six of these events, occurring in 4 patients, were considered related to study treatment. These included Grade 3 peripheral neuropathy in 3 patients, and Grade 2 pyrexia and Grade 3 lobar pneumonia in 1 patient each. Three separately reported but concurrent serious adverse events of Grade 4 neutropenia, Grade 4 febrile neutropenia and Grade 4 pneumonia were reported in another patient.

DCDS4501A in Combination with Rituximab

Adverse events regardless of relationship to study drug were reported in 6 patients receiving DCDS4501A at a dose of 2.4 mg/kg combined with rituximab in the Phase Ib cohorts. The most common of these adverse events in more than 2 patients were anaemia (2 patients), leukopenia (2 patients), neutropenia/febrile neutropenia (3 patients), nausea (3 patients), fatigue (2 patients), constipation (2 patients) and pyrexia (4 patients).

Grade ≥3 adverse events regardless of relationship to study drug were reported in 4 patients taking rituximab in combination with DCDS4501A. Grade 3 4 neutropenia was reported in 2 patients. One Grade 3 adverse event of streptococcal bacteremia unrelated to study treatment was reported in 1 patient. One Grade 4 adverse event of renal failure resulting from a septic arthritis and unrelated to study treatment was reported in 1 patient.

One serious adverse event of Grade 4 febrile neutropenia attributed to study treatment was reported among patients treated at the RP2D of 2.4 mg/kg single agent DCDS4501A. One serious adverse event of Grade 2 pyrexia related to study drug was reported in a patient receiving 2.4 mg/kg DCDS4501A combined with rituximab.

d. Efficacy

Investigator-based objective responses were observed in 28 of 49 (57%) patients treated with single-agent DCDS4501A and 7 of 9 patients (78%) treated with DCDS4501A

combined with rituximab. Among patients with relapsed/refractory DLBCL, objective responses were observed in 16 of 30 (53%; 4 CR, 12 PR) patients treated with DCDS4501A; 1 patient with DLBCL was treated with DCDS4501A combined with rituximab and achieved a PR. Among patients with relapsed/refractory iNHL, objective responses were observed in 7 of 14 (50%; 2 CR, 5 PR) patients treated with single-agent DCDS4501A and 5 of 5 (100%; 2 CR, 3 PR) patients treated with DCDS4501A plus rituximab. ~~To date, no formal analysis of anti-tumor activity has been performed for Study DCS4968g. Anti-tumor activity has been reported in patients treated with single-agent DCDS4501A as well as DCDS4501A when combined with rituximab.~~

SECTION 1.3.1: *Rationale for Assessing ADC Dose of 1.8 mg/kg Combined with Rituximab in iNHL*

Based on available Phase I data (see Section 1.2.1 and 1.2.2), both DCDT2980S and DCDS4501A as single-agents and combined with rituximab have shown early signs of clinical activity in heavily pretreated patients with relapsed/refractory NHL. However, early evidence in the Phase I studies indicate that duration of study treatment may be limited by tolerability to ADC. Specifically, for both ADCs, peripheral sensory neuropathy has been identified as a known risk (see Section 3.4.2). Notably, 4 of 7 and 5 of 11 discontinuations for adverse events in Studies DCT4862g and DCS4968g, respectively, were the result of peripheral neuropathy.

Because of the chronic course and incurability of iNHL, treatment paradigms are increasingly emphasizing tolerability to treatment in addition to efficacy. As both DCDT2980S and DCDS4501A have shown single-agent activity at the 1.8 mg/kg dose level (Advani et al. 2012; Palanca-Wessels et al. 2012), the purpose of enrolling additional cohorts of patients with follicular lymphoma is to determine whether lower doses of ADC in combination with standard doses of rituximab result in improved tolerability while maintaining efficacy in follicular lymphoma.

In contrast to iNHL, treatment paradigms in relapsed/refractory aggressive lymphomas such as DLBCL continue to place a premium on anti-tumor activity and higher tolerance for treatment-related toxicity given that durations of disease control and survival are substantially shorter and that treatment options are extremely limited. Early Phase I data suggest lower rates of study treatment discontinuation for adverse events among patients with DLBCL compared with patients with iNHL. Taken together with anti-tumor activity observed to date, the risk-benefit profile of the currently tested ADC dose of 2.4 mg/kg is considered acceptable

SECTION 2.3.3: Crossover Treatment Objective

- To preliminarily assess the safety and tolerability and anti-tumor activity of DCDT2980S and DCDS4501A, either as a single-agent or in combination with rituximab, as crossover treatment following disease progression on initial study treatment *(Note: This objective only applies to patients enrolled in Arms A and B [see Section 3.1])*

SECTION 3.1: DESCRIPTION OF THE STUDY

This is a Phase II, ~~randomized,~~ multicenter, open-label study. ~~No formal testing comparing the two treatment arms is planned.~~ A total of approximately *140*~~120~~*–160* patients (approximately *60–80*~~40~~ patients with relapsed or refractory follicular NHL and approximately 80 patients with relapsed/refractory DLBCL) will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

The study will be composed of a randomized portion and a nonrandomized portion, as illustrated in Figure 3.

Figure 3 (Study Schema) has been added.

SECTION 3.1.1: *Randomized Portion of the Study (Arms A and B)*

No formal testing comparing the two treatment arms in the randomized portion of the study is planned.

SECTION 3.1.2: *Nonrandomized Portion of the Study (Cohorts C and D)*

Only select investigator sites that have agreed to participate in the nonrandomized portion of the study will enroll patients into these cohorts.

Patients with relapsed or refractory follicular NHL will be enrolled in Cohorts C and D to receive rituximab (375 mg/m^2) combined with DCDT2980S or DCDS4501A at a dose of 1.8 mg/kg. The first day of treatment constitutes Day 1 of each cycle. A typical cycle will be 21 days in duration.

The opening of either or both cohorts will be at the Sponsor's discretion and only after the enrollment of follicular lymphoma patients into the randomized portion of the study is completed. Patients will not be randomized to receive one treatment or the other. It is anticipated that Cohort C and D will be opened sequentially.

SECTION 3.1.3: *All Patients*

All patients, regardless of assigned arm/cohort ~~Patients~~ will receive DCDT2980S or DCDS4501A and rituximab administered by IV infusion on a 21-day cycle…

SECTION 3.1.6: Crossover Treatment *(Randomized Patients Only)*

Patients *randomized* ~~assigned~~ to Arm A or Arm B who develop progressive disease may be eligible to receive crossover treatment consisting of rituximab and the other ADC, or the other ADC alone, e.g., Arm B treatment for patients who have disease progression while receiving Arm A treatment and vice versa, provided the following conditions are met:

- Patients who are enrolled into the nonrandomized portion of the study (Cohorts C and D) will not have the option to receive crossover treatment upon disease progression (see Section 3.2 for rationale).

SECTION 3.2: RATIONALE FOR STUDY DESIGN

The primary rationale for *the* ~~this~~ randomized non-comparative ~~Phase II study design~~ *portion of the study* is to assess clinical activity for the ADCs DCDT2980S and DCDS4501A in patients with relapsed/refractory NHL…

The primary rationale for the nonrandomized portion of the study is to assess the therapeutic index (i.e., the balance of efficacy and tolerability of DCDT2980S and DCDS4501A at a dose of 1.8 mg/kg in patients with relapsed or refractory follicular NHL). An informal comparison between patients with follicular NHL treated at the two doses of the ADC will help determine if tolerability is improved at the lower ADC dose without substantial compromise of efficacy.

SECTION 3.4.2.7: *Hyperglycemia*

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other antibody-drug conjugates using the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of anti-hyperglycemic medications.

SECTION 3.4.2.8: *Hepatotoxicity*

Hepatotoxicity is a potential risk of the ADCs. Definitive attribution of hepatotoxicity to the ADCs has not been established. Transient dose-related increases in hepatic enzyme levels were observed in rats treated with DCDT2980S and DCDS4501A. Elevations in transaminase and/or bilirubin levels requiring dose modifications have been reported in the ongoing clinical studies.

SECTION 4.1.1: Inclusion Criteria

- *For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one highly effective form of nonhormonal contraceptionor two effective forms of nonhormonal contraception,* ***including at least one method with a failure rate of <1% per year*** *through the course of study treatment and for at least 3 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later) in women and at least 5 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later) in men.*

  A woman is considered not to be of childbearing potential if she is postmenopausal, defined by amenorrhea of ≥12 months duration and age ≥45 years, or has undergone hysterectomy and/or bilateral oophorectomy.

  The following are considered highly effective forms of contraception: 1) true abstinence; 2) male sterilization (with postprocedure documentation of absence of sperm in the ejaculate). For female patients, the sterilized male partner should be the sole partner.

The following are considered effective forms of contraception: 1) intrauterine device (copper IUD or hormonal IUDs only) or intrauterine system; 2) condom with spermicidal foam/gel/film/cream/suppository; 3) occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.

Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later).

SECTION 4.1.2: Exclusion Criteria

- ~~For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one *highly effective* form of non-hormonal contraception or two *effective* forms of non-hormonal contraception through the course of study treatment and for at least 3 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later) in women and at least 5 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later) in men.~~

  ~~A woman is considered *not* to be of childbearing potential if she is postmenopausal, defined by amenorrhea of ≥12 months duration and age ≥45 years, or has undergone hysterectomy and/or bilateral oophorectomy.~~

  ~~The following are considered *highly effective* forms of contraception: 1) true abstinence; 2) male sterilization (with post-procedure documentation of absence of sperm in the ejaculate). For female patients, the sterilized male partner should be the sole partner.~~

  ~~The following are considered *effective* forms of contraception: 1) intrauterine device (copper IUD or hormonal IUDs only) or intrauterine system; 2) condom with spermicidal foam/gel/film/cream/suppository; 3) occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.~~

  ~~Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later).~~

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT

As described in Section 3.1.2, only select investigator sites that have agreed to participate in the nonrandomized portion of the study will enroll patients into these cohorts. Cohorts C and D will be opened sequentially following completion of the randomized portion of the study for follicular lymphoma patients.

SECTION 4.3.1.1: Formulation and Storage

b. DCDS4501A

DCDS4501A will be administered to patients by IV via syringe pump with IV infusion set containing a 0.22 µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight.

DCDS4501A vials must be refrigerated at 2–8°C (36–46°F) upon receipt until use. *DCDS4501A vials may be stored at room temperature (> 8°C to 25°C [46°F–77°F]) for up to 8 hours.* DCDS4501A should not be used beyond the expiration date provided by the manufacturer. Vial contents should not be frozen or shaken and should be protected from direct sunlight. *Vials are intended for single use only; therefore, any remaining solution should be discarded.*

~~DCDS4501A vials may be stored at~~ *Once the DCDS4501A dose solution has been prepared, the solution should be used within 4 hours at* room temperature (> 8°C to 25°C [46°F–77°F]) *or within 8 hours refrigerated at 2°C–8°C (36°F–46°F).*~~for up to 8 hours. DCDS4501A may be stored at room temperature (> 8°C to 25°C [46°F–77°F]) in an extension set and polypropylene syringe for up to 8 hours. The maximum allowed time in the syringe and extension set should not exceed 8 hours.~~ Because the Drug Product contains no preservatives, the Sponsor recommends using DCDS4501A in a syringe and extension set as soon as possible to reduce the risk of microbial contamination. ~~Vials are intended for single use only; therefore, any remaining solution should be discarded.~~

SECTION 4.3.1.2: Dosage and Administration

b. DCDS4501A-Specific Information

DCDS4501A will be administered to patients by IV via syringe pump with IV infusion set containing a 0.22 µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight. Compatibility testing has shown that DCDS4501A is stable in both syringes made of polypropylene (PP) and in standard extension sets with 0.22 µm in-line filter, when stored neat or diluted with 0.9% NaCl saline.
~~DCDS4501A will be administered to patients by IV infusion using standard medical syringes and syringe pumps. Compatibility testing has shown that DCDS4501A is stable in extension sets and polypropylene syringes. The Drug Product will be delivered by syringe pump via an IV infusion set containing a 0.22 µm in line filter with a final DCDS4501A volume determined by the dose and patient weight.~~

SECTION 4.3.1.3: Dosage Modification

Once dose reductions of DCDT2980S or DCDS4501A are made *for toxicity*, dose re-escalation will not be allowed. *Patients who are enrolled in the nonrandomized portion of the study (Cohorts C and D), are dosed at an ADC dose of 1.8 mg/kg, and have progressive disease in the absence of any drug-related toxicity may have their*

ADC dose increased to 2.4 mg/kg if it is felt that there is reasonable justification for ongoing clinical benefit. The decision to increase the dose must be made in consultation with and approval of the Medical Monitor.

SECTION 4.3.1.6: Neutropenia

- *For patients enrolled into the nonrandomized portion of the study (Cohorts C and D), dose modifications will not be allowed. Administration of therapeutic/prophylactic G-CSF and dose-schedule modifications as described above are allowed. Patients who have persistent or recurrent Grade 3–4 neutropenia as defined above should be discontinued from study treatment.*

SECTION 4.3.1.7: Peripheral Sensory Neuropathy

For patients enrolled into the nonrandomized portion of the study (Cohorts C and D), dose modifications will not be allowed. Patients who have Grade 2 or 3 peripheral sensory neuropathy as defined above should be discontinued from study treatment.

SECTION 4.3.1.8: *Hyperglycemia*

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other antibody-drug conjugates using the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation of improved anti-hyperglycemic medications (see Section 3.4.2.7).

For symptomatic fasting Grade 3 (>250–500 mg/dL) or asymptomatic Grade 4 (>500 mg/dL) hyperglycemia, medical management should be initiated immediately and consultation with a specialist should be considered. If the hyperglycemia persists for >1 week after initiation of management, dose modification, schedule modification, or discontinuation of study treatment should be considered. In these cases the study Medical Monitor should be consulted to assess the risk-benefit balance of continued study treatment.

SECTION 4.5.6: Follow-Up Assessments

Following discontinuation of study treatment, patients will be followed for survival approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

SECTION 4.10: STATISTICAL METHODS

The final analysis will be based on patient data collected through patient discontinuation or study discontinuation, whichever occurs first. The analyses will be based on the safety evaluable population defined as patients who received at least one dose of study treatment. All summaries will be presented according to the ~~assigned dose level regardless of crossover treatment~~ *disease specific cohort, treatment group, and assigned dose level.*

SECTION 4.10.1: Analysis of the Conduct of the Study

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, duration of malignancy, and baseline ECOG Performance Status, will be summarized using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables. All summaries will be presented overall and by treatment group*, assigned dose level,* and disease-specific cohort.

Study drug administration data will be listed by the disease-specific cohorts described in Section 3.1.1 and 3.1.2. Any dose modifications will be flagged. Means and standard deviations will be used to summarize the total doses of DCDT2980S, DCDS4501A and rituximab received. All summaries will be presented by treatment group*, assigned dose level,* and disease-specific cohort.

SECTION 4.10.2: Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, and changes in vital signs. All patients who receive any amount of DCDT2980S, DCDS4501A or rituximab will be included in the safety analysis and will be assigned to the treatment *group* ~~arm~~ based on the study treatment received. *Patients who have dose level changes from the initial assigned dose level will be summarized by the initial assigned dose level of DCDT2980S or DCDS4501A.*

SECTION 4.10.4: Activity Analyses

For the randomized portion of the study (Arms A and B), PFS is defined as the time from the date of randomization to the date of disease progression or death ~~within 30 days of the last study drug administration~~ *from any cause*, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the day of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. *For the nonrandomized portion of the study (Cohorts C and D), PFS is defined as the time from the date of study enrollment to the date of disease progression or death from any cause, whichever occurs first.*

For the randomized portion of the study (Arms A and B), o~~O~~verall survival is defined as the time from the date of randomization to the date of death from any cause. *For the nonrandomized portion of the study (Cohorts C and D), overall survival is defined as the time from the date of study enrollment to date of death from any cause.*

SECTION 4.10.7: Determination of Sample Size

For the randomized portion of the study (Arms A and B), a~~A~~ target of 120 patients will be enrolled in two separate cohorts of patients (40 in the follicular NHL cohort and 80 in the DLBCL cohort)…

This is a non-comparative hypothesis-generating study. There is no formal hypothesis testing planned to compare the ~~two~~ treatment arms. *Specifically, for the randomized portion of the study,* ~~and~~ there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms.

SECTION 5.1.3: *Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)*

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions), irrespective of regulatory seriousness criteria. Adverse events of special interest for this study include the following:

- *Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.1.6; treatment-emergent ALT or AST >3 ×baseline value in combination with total bilirubin >2 ×ULN [of which 35% is direct bilirubin])*
- *Suspected transmission of an infectious agent by the study drug*
- *Grade ≥2 motor neuropathy*
- *Grade ≥2 infusion reactions*

SECTION 5.3.1.5: *Abnormal Vital Sign Values*

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- *Accompanied by clinical symptoms*
- *Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)*
- *Results in a medical intervention (including a diagnostic evaluation not mandated in this protocol) or a change in concomitant therapy*
- *Clinically significant in the investigator's judgment*

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

SECTION 5.3.1.6: *Abnormal Liver Function Tests*

The finding of an elevated ALT or AST (>3 ×baseline value) in combination with either an elevated total bilirubin (>2 ×ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- *Treatment-emergent ALT or AST >3 ×baseline value in combination with total bilirubin >2 ×ULN (of which 35% is direct bilirubin)*
- *Treatment-emergent ALT or AST >3 ×baseline value in combination with clinical jaundice*

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2)

SECTION 5.4.2: ~~Reporting Requirements for All SAEs~~ *Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest*

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to the Sponsor's Safety Risk Management department by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

~~Investigators will submit reports of all SAEs, regardless of attribution, to Genentech within 24 hours of learning of the events. For initial SAE reports, investigators should record all case details that can be gathered within 24 hours on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Genentech's Drug Safety Department. In the event that the EDC system is unavailable,~~

~~a paper Serious/Non-Serious Expedited Adverse Event CRF and Fax Cover Page should be completed and faxed immediately to Genentech's Drug Safety Department or its designee at the fax numbers indicated below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.~~

REFERENCES

The following references have been added:

- *Advani et al. 2012*
- *Palanca-Wessels et al. 2012*

APPENDIX A-1: Study Flowchart: Initial Study Treatment

The Study Flowchart has been revised to reflect the changes to the protocol.

APPENDIX A-2: Study Flowchart: Crossover Treatment *(Patients Randomized to Arms A or B Only)*

The Study Flowchart has been revised to reflect the changes to the protocol.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT FINALIZATION SIGNATURE PAGE

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF DCDT2980S IN COMBINATION WITH RITUXIMAB OR DCDS4501A IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
EUDRACT NUMBER:	2011-004377-84
STUDY DRUG:	DCDT2980S; DCDS4501A
IND:	107713
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	27 July 2012
DATE AMENDED:	Version 1: See electronic date on cover page

This protocol was finalized on the date shown above.

[redacted]

[redacted], M.D.

(See electronic date stamp on cover page)
Date

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF DCDT2980S IN COMBINATION WITH RITUXIMAB OR DCDS4501A IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
EUDRACT NUMBER:	2011-004377-84
STUDY DRUG:	DCDT2980S; DCDS4501A
IND:	107713
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	27 July 2012
DATE AMENDED:	Version 1: See electronic date on cover page

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return a copy of the form to the CRO Monitor at your site. Please retain the original for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE II TRIAL EVALUATING THE SAFETY AND ACTIVITY OF DCDT2980S IN COMBINATION WITH RITUXIMAB OR DCDS4501A IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA**
PROTOCOL NUMBER:	GO27834
EUDRACT NUMBER:	2011-004377-84
STUDY DRUG:	DCDT2980S; DCDS4501A
PHASE:	II
INDICATION:	Relapsed or refractory B-cell NHL
IND:	107713
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	27 July 2012
DATE AMENDED:	Version 1: See electronic date on cover page

Objectives

Primary Objectives

The primary objectives of this study are the following:

- To assess the safety and tolerability of the combination of DCDT2980S and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the safety and tolerability of the combination of DCDS4501A and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDT2980S and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and rituximab in patients with relapsed or refractory follicular NHL and DLBCL

Secondary Objectives

The secondary safety objectives of this study are the following:

- To assess the incidence of antibody formation to DCDT2980S and DCDS4501A
- To compare the safety and tolerability of the combination of DCT2980S and rituximab and DCDS4501A and rituximab

Activity Objective

The secondary activity objective of the study is the following:

- To compare the anti-tumor activity of the combination of DCT2980S and rituximab and DCDS4501A and rituximab

Pharmacokinetic Objectives

The PK objectives of this study are the following:

- To characterize the pharmacokinetics of DCDT2980S and rituximab in patients with relapsed or refractory NHL when the two drugs are given in combination
- To characterize the pharmacokinetics of DCDS4501A and rituximab in patients with relapsed or refractory NHL when the two drugs are given in combination

Study Design

This is a Phase II, multicenter, open-label study. A total of approximately *140–160* patients (approximately *60–80* patients with relapsed or refractory follicular NHL and approximately 80 patients with relapsed/refractory DLBCL) will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

Randomized Portion of the Study (Arms A and B)

Following determination of eligibility, patients within each disease group will be randomized in a 1:1 ratio to receive one of two treatments:

- Arm A: Rituximab (375 mg/m^2) followed by DCDT2980S (2.4 mg/kg) every 21 days;
- Arm B: Rituximab (375 mg/m^2) followed by DCDS4501A (2.4 mg/kg) every 21 days

The first day of treatment constitutes Day 1 of each cycle. A typical cycle is 21 days in duration.

A dynamic hierarchical randomization scheme will be employed with respect to the following stratification factors:

- For patients with follicular lymphoma (see Section 3.1.1 for definitions)

  Rituximab refractory disease (no response or disease relapse < 6 months from last rituximab treatment) vs. rituximab relapsed disease (disease relapse after response ≥ 6 months from last rituximab treatment)

- For patients with DLBCL (see Section 3.1.2 for definitions)

  Second-line vs. third-line (or beyond) therapy

  For second-line patients, disease relapse or no objective response (CR, CRu or PR) <12 months from the start of initial therapy versus disease relapse, after initial objective response (CR, CRu or PR), ≥12 months from start of initial therapy

  For third-line patients, failure to achieve a CR or progression < 6 months of start of most recent therapy versus CR or progression ≥ 6 months from start of most recent therapy

No formal testing comparing the two treatment arms in the randomized portion of the study is planned.

Nonrandomized Portion of the Study (Cohorts C and D)

Only select investigator sites that have agreed to participate in the nonrandomized portion of the study will enroll patients into these cohorts.

Patients with relapsed or refractory follicular NHL will be enrolled in Cohorts C and D to receive rituximab (375 mg/m^2) combined with DCDT2980S or DCDS4501A at a dose of 1.8 mg/kg. The first day of treatment constitutes Day 1 of each cycle. A typical cycle will be 21 days in duration.

The opening of either or both cohorts will be at the Sponsor's discretion and only after the enrollment of follicular lymphoma patients into the randomized portion of the study is completed. Patients will not be randomized to receive one treatment or the other. It is anticipated that Cohort C and D will be opened sequentially.

All Patients

All patients, regardless of assigned arm/cohort will receive DCDT2980S or DCDS4501A and rituximab administered by IV infusion on a 21-day cycle. For the first two cycles, rituximab will be administered by IV infusion on Day 1 and DCDT2980S or DCDS4501A will be administered by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this instance, rituximab will be administered first, followed by DCDT2980S or DCDS4501A. In certain circumstances, e.g., infusion-related reactions requiring interruption or slowing of infusion rate, rituximab may be administered over 2 days, e.g., Day 1 and Day 2 of the cycle; in this case, DCDT2980S or DCDS4501A may be administered on Day 2 following completion of the rituximab infusion or on Day 3 of the cycle.

Patients may receive treatments for up to 1 year (17 cycles on an every-21-day schedule) if not discontinued due to significant toxicity, disease progression, or withdrawal from study.

Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in Appendices A-1, A-2, and A-3. Initial response assessments in this study will be performed every 3 months from the initiation of therapy until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). Additional response assessments for patients who proceed to crossover treatment (see Section 3.1.3) will be performed as described in Appendix A-2; response assessments for patients who discontinue study treatment (both initially assigned treatment and crossover treatment) for reasons other than disease progression will be performed as described in Appendix A-3.

Responses to study treatment will be based on investigator assessments. In addition, tumor assessment data will be transmitted to an Independent Review Facility (IRF) for collection and possible independent review.

Follicular NHL Cohort

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed to regimens containing rituximab, defined as documented history of response (complete response [CR], unconfirmed CR [CRu], or partial response [PR]) of $\geq$ 6 months in duration from completion of all prior rituximab-containing regimens. A rituximab-containing regimen is defined as rituximab as a single agent during induction and/or maintenance, or in combination with other agents during induction and/or maintenance.
- Refractory to any prior regimen containing rituximab, defined as no response to, or progression within 6 months of completion of, the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:

  Patients with progressive disease while receiving rituximab monotherapy, rituximab combined with chemotherapy, or rituximab maintenance therapy; patients must have received at least one full dose (375 mg/m^2) of rituximab

  Patients with no objective response (PR or CR) to a rituximab-containing regimen consisting of at least 4 weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

  Patients with disease relapse, after having achieved an objective response, within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Enrollment of patients with refractory disease as defined above may be limited to no greater than 60% of the total Follicular NHL cohort, in order to avoid overrepresentation of the refractory disease population.

DLBCL Cohort

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high dose therapy with autologous stem cell rescue/stem cell transplant (SCT) as determined by the investigator will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) $<$ 12 months from start of initial therapy (2L refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response $\geq$ 12 months from start of initial therapy (2L relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) $<$ 6 months from start of prior therapy (3L + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response $\geq$ 6 months from start of prior therapy (3L+ relapsed)

Enrollment to any of the above four categories may be limited to no greater than 40% of the DLBCL cohort—and to no more than 60% of the two refractory categories combined—in order to avoid overrepresentation of any specific subpopulation, refractory patients in particular.

Crossover Treatment ***(Randomized Patients Only)***

Patients *randomized* to Arm A or Arm B who develop progressive disease may be eligible to receive crossover treatment consisting of rituximab and the other ADC, or the other ADC alone, e.g., Arm B treatment for patients who have disease progression while receiving Arm A treatment and vice versa, provided the following conditions are met:

- Patients must not have experienced a toxicity requiring the discontinuation of DCDT2980S/DCDS4501A treatment OR experienced toxicity during the last dose of study treatment that would preclude treatment with the crossover regimen.

  Patients who had modifications to dosing and/or schedule on the initial study treatment will be permitted to receive crossover treatment in the absence of toxicities on the modified dose and/or schedule. The dose and schedule of crossover treatment will be determined by the investigator and the Medical Monitor.

  Patients who had rituximab discontinued and continued on single-agent DCDT2980S/DCDS4501A treatment may receive crossover treatment of single-agent DCDS4501A/ DCDT2980S
- Patients must have radiographically documented disease progression
- Patients must meet all inclusion and exclusion criteria described in Sections 4.1.1 and 4.1.2, except for those related to prior rituximab treatment.
- Acceptable toxicity: All study drug–related adverse events from the initial study treatment must have decreased to Grade 1 or baseline grade on or before the first day of treatment on the crossover regimen. Exceptions may be allowed after a careful assessment and discussion of the risk-benefit balance with the patient by the investigator and approval from the Medical Monitor.
- Administration of crossover treatment must be in the best interests of the patient as determined after a careful assessment and discussion of risk-benefit balance with the patient by the investigator and approval from the Medical Monitor.
- A tumor biopsy will be required for patients with safely accessible site of disease, defined as requiring only local anesthesia and in general excluding brain, lungs or any internal organs that may subject patients to significant risk.

  Patients for whom a safely accessible site of disease is not present may still receive crossover treatment without undergoing a biopsy. Eligibility to receive crossover treatment should be discussed with and approved by the Medical Monitor.

  A tumor biopsy of a safely accessible site of disease is optional for patients who are not eligible for study cross over.

Patients who are determined to be eligible for study crossover will be treated as follows:

- Assessments obtained at the initial study treatment discontinuation visit may be used as screening assessments for crossover treatment. The following re-screening assessments must be repeated/obtained within 1 week prior to starting treatment on the crossover regimen in order to re-establish baseline pretreatment clinical and disease status: targeted physical exam, ECOG status and hematology and serum chemistry laboratories.

  Re-screening tests for Hepatitis B and C do not need to be performed unless there is clinical suspicion of Hepatitis B and/or C positivity.

  A radiographic tumor assessment must also be performed, unless already done to document disease progression, within 6 weeks prior to starting crossover treatment.
- Crossover treatment will begin no later than 42 days after the last dose of the prior study treatment.

Patients will be treated with the crossover treatment until a second disease progression event relative to the tumor assessment documenting progressive disease on the initial study treatment, clinical deterioration and/or intolerance to the crossover treatment for up to a maximum of 1 year (17 cycles on an every-21-day schedule). Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in Appendices A-2. Response assessments for patients who discontinue study treatment for reasons other than disease progression will be performed as described in Appendix A-3.

Clinical data and exploratory data derived from tumor biopsies obtained prior to crossover treatment will be monitored on an ongoing basis. Genentech has the right to restrict or suspend enrollment into crossover treatment at any time. Reasons for this may include, but are not limited to, the following:

- The incidence or severity of adverse events during crossover treatment indicates a potential safety hazard to patients.
- Patient enrollment into crossover treatment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- *Patients who are enrolled into the nonrandomized portion of the study (Cohorts C and D) will not have the option to receive crossover treatment upon disease progression.*

Outcome Measures

Safety Outcome Measures

The safety and tolerability of the combination of DCDT2980S and rituximab and DCDS4501A and rituximab will be assessed using the following safety outcome measures:

- Incidence, nature, and severity of adverse events
- Incidence of anti-DCDT2980S or anti-DCDS4501A antibodies
- Changes in vital signs
- Changes in laboratory values

Pharmacokinetic/Pharmacodynamic Outcome Measures

The following PK parameters will be derived from the serum concentration–time profiles of total antibody (the sum of conjugated and unconjugated antibody), including rituximab, and plasma concentration-time profiles of antibody conjugated-MMAE (acMMAE) and free MMAE following administration of DCDT2980S or DCDS4501A, when appropriate as data allow:

- Total exposure (area under the concentration-time curve [AUC])
- Maximum plasma and serum concentration (C_{max})
- Clearance (CL)
- Terminal half-life (t1/2)
- Steady state volume of distribution (Vss).

Compartmental, non-compartmental, and/or population methods may be used. Other parameters, such as accumulation ratio and trough plasma and serum concentration (C_{min}), may also be calculated.

The following PD outcome measures will be assessed when appropriate, as data allow:

- Peripheral blood B-cell depletion and recovery. For each visit at which CD19+ B-cell measurements are taken, B-cell data will be listed for each patient by dose level as follows:

  Absolute blood cell counts

  Percent change relative to the baseline blood counts

  CD19+ B-cell recovery, defined as the timepoint when the values return to baseline levels or $\geq$ 50% of baseline levels

Activity Outcome Measures

The following activity outcome measures will be assessed:

- Objective response, defined as a PR or CR
- Duration of objective response, defined as the first occurrence of a documented objective response until the time of relapse or death from any cause
- Progression-free survival (PFS), defined as the date of randomization to the first occurrence of progression or death within 30 days of the last administration of study drug, whichever occurs first
- Overall survival (OS), defined as the time from the date of randomization to the date of death from any cause

Objective response and disease progression will be determined using standard criteria for NHL (Cheson et al. 2007; see Appendix C).

Safety Plan

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

Safety will be evaluated through the monitoring of the following:

- Serious adverse events that are attributed to protocol-mandated interventions from the time of signing informed consent until the first dose of study treatment on Cycle 1, Day 1
- All adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A or rituximab whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A or rituximab whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from the last dose of DCDT2980S, DCDS4501A or rituximab whichever is later, including doses that were administered as part of crossover treatment, and which is judged to be caused by DCDT2980S, DCDS4501A or rituximab, regardless of time of onset
- Measurements of protocol-specified hematology and clinical chemistry laboratory values
- Measurements of protocol-specified vital signs
- Assessment of ECGs
- Assessment of physical findings on clinical physical examinations

Patients who have an ongoing study drug-related adverse event will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, when it has been determined that the study treatment or participation is not the cause of the adverse event, or the study is terminated.

See Section 5.2.3 for assessment of causality for adverse events.

INTERNAL MONITORING COMMITTEE (IMC)

This study will employ an Internal Monitoring Committee (IMC). The purpose of the IMC will be to make recommendations regarding study conduct on the basis of trial safety data to ensure patient safety while receiving study treatment.

The IMC will include a sponsor Medical Monitor not affiliated with the study, Drug Safety Scientist, biostatistician, and statistical programmer. Representatives from other Sponsor functional areas may be included as additional ad hoc members.

In addition to the ongoing assessment of the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities by the Investigator and the Medical Monitor, the IMC will review the aforementioned data at least twice during the study. The first planned review will occur after approximately 10 patients are randomized and have at least 6 weeks follow-up and the next formal review will occur when approximately 60 patients are randomized and have at least 6 weeks follow-up. Additionally, the IMC will meet as needed at the request of the Medical Monitor, e.g., based on unexpected safety signals. The IMC may make recommendations regarding study conduct, including but not limited to: performing additional safety analyses, amending the study protocol, holding patient enrollment to one or both treatment arms pending further safety evaluations, holding/discontinuing study treatment, or terminating the study.

Complete details of the IMC will be described in the IMC charter.

Risks Associated with DCDT2980S and DCDS4501A

The clinical safety profile of DCDT2980S and DCDS4501A based on clinical data obtained in the ongoing Phase I studies are summarized in Sections 1.2.1.2 and 1.2.2.2. Based on clinical data to date, the following known and suspected risks are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Sections 4.3.1 and 4.3.2. Refer also to the Investigator Brochure for complete and updated details.

Infusion-Related Events

Some monoclonal antibodies may be associated with the development of allergic or anaphylactic reactions, to either the active protein or excipients. True allergic/anaphylactic reactions are rare after the first dose of a product, as they require prior sensitization. Patients with true allergic/anaphylactic reactions should not receive further doses of the product.

Monoclonal antibodies may also be associated with reactions that are clinically indistinguishable from true allergic/anaphylactic reactions, but which are mediated through direct release of cytokines or other pro-inflammatory mediators. Such reactions are often termed infusion-related reactions. Infusion-related reactions typically occur with the first infusion of a monoclonal antibody product and are generally less frequent and/or less severe with subsequent infusions. They can often be managed by slowing the infusion rate and/or pre-treatment with various medications.

Allergic/anaphylactic reactions and infusion-related reactions typically begin during or within several hours of completing the infusion. The onset of symptoms may be rapid, and some reactions may be life threatening.

Patients should be monitored for these types of reactions during and after receiving DCDT2908S and DCDS4501A. DCDT2980S and DCDS4501A should be administered in an environment under close supervision of a physician and where full resuscitation facilities are immediately available. Specific guidelines for additional precautions to be taken during and following DCDT2980S and DCDS4501A administration are provided in Sections 4.3.1.5.

Tumor Lysis Syndrome

There is a potential risk of tumor lysis syndrome (TLS) if treatment with DCDT2980S or DCDS4501A results in the rapid destruction of a large number of tumor cells. If any evidence of this occurs during the study, tumor lysis prophylaxis measures will be instituted. Patients who are considered to have a high tumor burden, e.g., lymphocyte count $\geq$ 25 x 109/L or bulky lymphadenopathy and who are considered to be at risk for tumor lysis by the investigator will receive tumor lysis prophylaxis, e.g., allopurinol $\geq$ 300 mg/day orally or a suitable alternative treatment according to institutional practice starting 12–24 hours prior to study treatment, and must be well hydrated prior to the initiation of study treatment at Cycle 1, Day 1. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion as deemed appropriate by the investigator.

Bone Marrow Toxicity/*Neutropenia*

Based on preclinical toxicity studies in rats and cynomolgus monkeys and clinical data from the ongoing Phase I studies DCT4862g and DCS4968g, neutropenia has been identified as a known risk (adverse drug reaction) of both DCDT2908S and DCDS4501A. Neutropenia and neutropenia-associated events were reversible but in some cases resulted in protocol-mandated dose reductions and/or delays.

Adequate hematologic function should be confirmed before initiation of study treatment. Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Treatment for hematologic toxicities may be delayed or modified as described in Section 4.3.1.

The use of G-CSF for neutropenia is described in Section 4.3.1.6. Transfusion support for anemia and thrombocytopenia is also permitted at the discretion of the treating physician.

Immunogenicity

As expected with any recombinant antibody, DCDT2980S and DCDS4501A may elicit an immune response and patients may develop antibodies against DCDT2980S and DCDS4501A. Patients will be closely monitored for any potential immune response to DCDT2980S and DCDS4501A. Appropriate screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with DCDT2980S or DCDS4501A. Considering the historically low immunogenicity rate of rituximab in NHL patients, ATAs against rituximab will not be monitored in this study.

Peripheral Sensory Neuropathy

Based on clinical data from the ongoing Phase I studies DCT4862g and DCS4968g and data from brentuximab vedotin, an anti-CD30-vc-MMAE ADC (see Section 3.4.2) peripheral sensory neuropathy has been identified as a known risk (adverse drug reaction) for both DCDT2980S and DCDS4501A.

Patients should be monitored for signs of neuropathy or worsening neuropathy and appropriate action taken per protocol guidelines. Study treatment dose and schedule modifications for significant and prolonged neuropathic toxicity and dose-reduction are described in Section 4.3.1.7.

Reproductive Toxicity

Adverse effects on human reproduction and fertility are anticipated with the administration of DCDT2980S and DCDS4501A given the mechanism of action of MMAE. Standard exclusion criteria will be used to ensure that patients of childbearing potential (male or female) are using adequate contraceptive methods.

Hyperglycemia

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other antibody-drug conjugates using the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of anti-hyperglycemic medications.

Hepatotoxicity

Hepatotoxicity is a potential risk of the ADCs. Definitive attribution of hepatotoxicity to the ADCs has not been established. Transient dose-related increases in hepatic enzyme levels were observed in rats treated with DCDT2980S and DCDS4501A. Elevations in transaminase and/or bilirubin levels requiring dose modifications have been reported in the ongoing clinical studies.

Study Treatment

DCDT2980S-Specific Information

DCDT2980S will be administered to patients by IV infusion. Compatibility testing has shown that DCDT2980S is stable when diluted in polyvinyl chloride (PVC) bags to a concentration at or above 0.04 mg/mL in 0.9% NaCl diluent. The Drug Product will be delivered following dilution in 0.9% NaCl with a final DCDT2980S concentration determined based on dose and patient weight. The study drug will be diluted in a PVC bag and delivered using a 0.22µm in-line filter on the IV infusion set.

Additional information/instructions regarding study drug administration will be provided in the Pharmacy Binder.

DCDS4501A-Specific Information

DCDS4501A will be administered to patients by IV via syringe pump with IV infusion set containing a 0.22 µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight. Compatibility testing has shown that DCDS4501A is stable in both syringes made of polypropylene (PP) and in standard extension sets with 0.22 µm in-line filter, when stored neat or diluted with 0.9% NaCl saline.

Additional information/instructions regarding study drug administration will be provided in the Pharmacy Binder.

General Information

The total dose of DCDT2980S and DCDS4501A for each patient will depend on the patient's weight within 96 hours prior to Day 1 of each cycle. The patient weight obtained during screening may be used for dose determination at all treatment cycles; if the patient's weight within 96 hours prior to Day 1 of a given treatment cycle differs by >10% from the weight obtained during screening, then the new weight should be used to calculate the dose.

For both DCDT2980S and DCDS4501A, the initial dose will be administered to well-hydrated (based on clinical judgment) patients over 90 (± 10) minutes. Pre-medication with acetaminophen or paracetamol (e.g., 500–1000 mg) and diphenhydramine (e.g., 50–100 mg) per institutional standard practice may be administered prior to each infusion. Administration of corticosteroids is permitted at the discretion of the treating physician. For patients who do not receive pre-medications prior to the first dose of DCDT2980S and who develop an infusion related reaction during the first dose should receive pre-medications prior to subsequent doses (see Table 1).

The DCDT2980S/DCDS4501A infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. Following the initial dose, patients will be observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If the infusion is well-tolerated, subsequent doses of DCDT2980S/DCDS4501A may be administered over 30 (± 10) minutes, followed by a 30-minute observation period post-infusion.

For further details, see Section 4.3

Concomitant Therapy and Clinical Practice

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the end of study visits. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF).

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Concomitant use of hematopoietic growth factors is allowed in accordance with instructions provided in the package inserts.

Patients who experience infusion-related temperature elevations of > 38.5°C (> 101.3°F) or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol (≥ 500 mg) and/or H1 and H2 histamine-receptor antagonists (e.g., diphenhydramine, ranitidine). Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with additional supportive therapies (e.g., supplemental oxygen, β2-agonists, and/or corticosteroids) as clinically indicated according to standard clinical practice.

Infusion reaction prophylaxis with medications (e.g., acetaminophen/paracetamol, antihistamines, and/or corticosteroids) may be instituted at any point in the study if it is determined to be in the best interest of the patient based on observation of IRRs in patients already enrolled in the study. Patients with Grade 3 hypotension or fever must be pre-medicated prior to retreatment. Patients with hypotension requiring vasopressor support, or with Grade 3 wheezing, hypoxia, or generalized urticaria, must be permanently discontinued from study treatment.

Excluded Therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy
- Immunotherapy including immunosuppressive therapy
- Radioimmunotherapy
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Biologic agents (other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts); guidelines for the use of G-CSF are detailed in Section 4.3.1.6 and Appendix F.
- Any therapies intended for the treatment of lymphoma or leukemia, whether approved by local regulatory authorities or investigational

Patients who require the use of any of these agents will be discontinued from all study treatment. Patients who are discontinued from study treatment will be followed for safety outcomes for 30 days following the patient's last dose of DCDT2980S or DCDS4501A or rituximab, whichever is later, or until the patient receives another anti-cancer therapy whichever occurs first.

Statistical Methods

Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, and changes in vital signs. All patients who receive any amount of DCDT2980S, DCDS4501A or rituximab will be included in the safety analysis and will be assigned to the treatment *group* based on the study treatment received. *Patients who have dose level changes from the initial assigned dose level will be summarized by the initial assigned dose level of DCDT2980S or DCDS4501A.*

All adverse event data will be listed by study site, patient number, treatment group, disease-specific cohort, and cycle. All adverse events occurring on or after treatment on Day 1 of Cycle 1 will be summarized by mapped terms, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade. In addition, all serious adverse events, including deaths will be listed separately and summarized.

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to DCDT2980S and DCDS4501A will be summarized.

Activity Analysis

Best overall response, duration of response, and PFS will be listed for all patients.

Objective response rate from the initial study treatment will be calculated based on data from patients who received study treatment and had at least one post-baseline response assessment. Objective response is defined as complete response (CR) or partial response (PR) as determined by the investigator, based on physical examinations, radiographic scans, and bone marrow examinations, using modified response criteria for NHL (Cheson et al. 2007; see Appendix C), and confirmed by repeat assessments $\geq$ 4 weeks after initial documentation. Any patient with insufficient data to determine response will be classified as a non-responder.

For patients with DLBCL, primary assessment of tumor response will be based on diagnostic imaging scans, e.g., CT and/or MRI, and PET scans. For patients with FL, primary assessment of response will be based on CT scans only; the assessment of response in FL based on PET scans will be performed for exploratory purposes only.

Among patients with an objective response, duration of response will be defined as the time from the initial CR or PR to the time of disease progression or death. If a patient does not experience death or disease progression before the end of the study, duration of response will be censored at the day of the last tumor assessment.

For the randomized portion of the study (Arms A and B), PFS is defined as the time from the date of randomization to the date of disease progression or death *from any cause*, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the day of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. *For the nonrandomized portion of the study (Cohorts C and D), PFS is defined as the time from the date of study enrollment to the date of disease progression or death from any cause, whichever occurs first.*

*For the randomized portion of the study (Arms A and B), o*verall survival is defined as the time from the date of randomization to the date of death from any cause. *For the nonrandomized portion of the study (Cohorts C and D), overall survival is defined as the time from the date of study enrollment to date of death from any cause.*

Missing Data

For the endpoint of objective response, patients without a post-baseline tumor assessment will be considered non-responders in the all-treated population analysis.

For duration of response and PFS, data from patients who are lost to follow-up will be included in the analysis as censored observations on the last date that the patient is known to be progression free, defined as the date of the last tumor assessment, or, if no tumor assessments were performed, as the date of last study treatment plus 1 day.

Compliance to PRO data collection will be reported with summary statistics, including frequencies of reasons for non-compliance such as patient refusal to complete PRO data collection.

Determination of Sample Size

For the randomized portion of the study (Arms A and B), a target of 120 patients will be enrolled in two separate cohorts of patients (40 in the follicular NHL cohort and 80 in the DLBCL cohort). Genentech has judged this sample size to provide sufficient precision in estimating the anti-tumor activity of DCDT2980S combined with rituximab or DCDS4501A combined with rituximab as measured by objective response. For example, with the assumption of an observed response rate of 40%, a 90% confidence interval for the response rate would be approximately 22%–58% (i.e., 40% $\pm$ 18%) for the follicular NHL cohort and approximately 27%–53% (i.e., 40% $\pm$ 13%) for the DLBCL cohort.

This is a non-comparative hypothesis-generating study. There is no formal hypothesis testing planned to compare the treatment arms. *Specifically, for the randomized portion of the study,* there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADC	antibody–drug conjugate
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
anti-HBc	Hepatitis B core antibody
AST	aspartate aminotransferase
ATA	Anti-therapeutic antibody
AUC	area under the concentration-time curve
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma and serum concentration
C_{min}	trough plasma and serum concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	cyclophosphamide, vincristine, and prednisone
DLBCL	diffuse large B-cell lymphoma
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent *assay*
EMA	European Medicines Agency
FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration
FL	follicular lymphoma
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HNSTD	highest non-severely toxic dose
ICH	International Conference on Harmonisation
IgG1	immunoglobulin-G1
IMC	Internal Monitoring Committee
IND	Investigational New Drug
iNHL	*indolent*
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IXRS	Interactive Voice and Web Response System
LC-MS/MS	Liquid chromatography–tandem mass spectrometry
MCL	mantle cell lymphoma
MC-VC-PABC	maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl
MDASI	M.D. Anderson Symptom Inventory
MFI	mean fluorescence intensity
MMAE	monomethyl auristatin E
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PET	positron emission topography
PD	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukencephalopathy
PR	partial response
PT	prothrombin time
PVC	polyvinyl chloride
RP2D	recommended phase II dose
SAE	serious adverse event
SCT	stem cell transplant
SD	stable disease

Abbreviation	Definition
SDV	source data verification
SLL	small lymphocytic lymphoma
SWFI	Sterile Water for Injection
$t_{1/2}$	terminal half-life
TLS	tumor lysis syndrome
ULN	upper limit of normal
V_{ss}	steady state volume of distribution

1. BACKGROUND

1.1 BACKGROUND ON DISEASE

B-cell lymphoproliferative disorders are a heterogeneous group of malignancies, ranging from slow-growing indolent and incurable diseases with a median survival of 8–10 years (such as follicular non-Hodgkin's lymphoma [NHL]) to more aggressive intermediate- to high-grade lymphomas (such as diffuse large-cell lymphoma), which can have a median survival of 6 months if left untreated or long-term remission in more than 50% of patients with appropriate treatment. Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL accounting for approximately 30%–40% of all new patients, whereas follicular lymphoma (FL) accounts for approximately 20%–25% of new lymphomas, respectively.

Despite advances in the clinical outcomes of patients with NHL using treatments such as the CD20-specific monoclonal antibody rituximab (Rituxan®, MabThera®) in combination with chemotherapy, indolent B-cell malignancies remain incurable as are approximately half of aggressive NHL patients. Thus, there is still a need for treatments that can be combined with chemoimmunotherapy and can significantly extend disease-free and overall survival in these patients, with at least acceptable, if not superior, safety profiles.

1.2 BACKGROUND ON THE MOLECULES

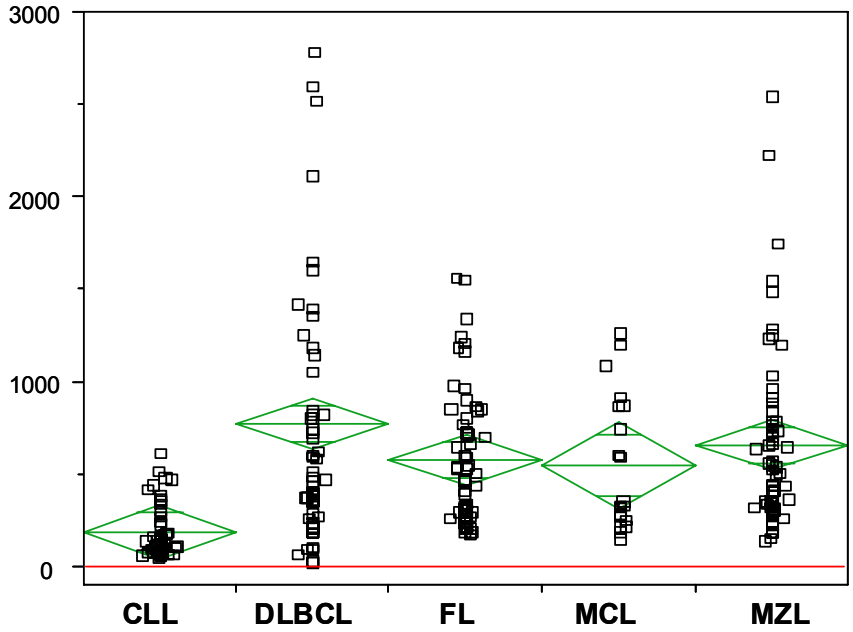
1.2.1 DCDT2980S

1.2.1.1 Background and Preclinical Data

CD22 is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of the B-cell–derived malignancies, including nearly all NHL and chronic lymphocytic leukemia (CLL) samples tested (see Figure 1). Antibodies bound to CD22 are rapidly internalized, making CD22 ideally suited for targeted delivery of cytotoxic agents (Shan and Press 1995).

DCDT2980S is an antibody–drug conjugate (ADC) that consists of a potent anti-mitotic agent, monomethyl auristatin E (MMAE) conjugated to a humanized immunoglobulin-G1 (IgGI) anti-CD22 monoclonal antibody, MCDT2219A, via a protease-labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl (MC-VC-PABC). MMAE has a mode of action similar to vincristine, which is a component of standard chemotherapy used in lymphoma therapy. This therapeutic approach takes advantage of the specific targeting capability of the antibody and the cytotoxic activity of MMAE. Following internalization, the MMAE is deconjugated from DCDT2980S by lysosomal enzymes, binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth and induction of apoptosis (Doronina et al. 2003).

Figure 1 CD22 Expression Levels on B-Cell Tumor Cells



CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MFI = mean fluorescence intensity; MZL = marginal zone lymphoma.
CD22 expression levels (MFI) on B-cell tumor cells were assessed by flow cytometry in patients diagnosed with the following B-cell lymphomas: CLL (n = 49), DLBCL (n = 59), FL (n = 58), MCL (n = 20), and MZL (n = 60).

Comprehensive pharmacology, pharmacokinetic (PK), pharmacodynamic (PD), and toxicology evaluations were conducted to support the use of DCDT2980S in clinical trials. DCDT2980S binds human CD22 with a high affinity (equilibrium dissociation constant [K_d] = 1.7 ± 0.2 nM) and showed similar binding affinity to cynomolgus monkey CD22. No binding activity was observed with mouse and rat peripheral blood mononuclear cells (PBMCs).

The unconjugated antibody MCDT2219A did not appear to induce antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) in vitro. In contrast, DCDT2980S displayed potent and selective inhibition of cell proliferation in vitro (50% of the maximal inhibitory concentration [IC_{50}] = 0.33 nM) by cell viability assays. Efficacy studies conducted in murine xenograft models of human lymphoma (CD22-positive WSU-DLCL2 and BJAB cell lines) showed that a single dose of DCDT2980S resulted in regression of tumor growth at doses ranging from 1 to 4 mg/kg. PD studies with DCDT2980S showed that a single dose of 1–6 mg/kg resulted in partial depletion of peripheral blood B-cells in cynomolgus monkeys with a corresponding depletion in germinal center B-cells in lymphoid tissue.

The PK profiles of DCDT2980S were observed to be linear in rodents and moderately non-linear in cynomolgus monkeys over the tested dose range. The non-linear

clearance (CL) observed in cynomolgus monkeys with DCDT2980S is likely due to the contribution of B-cell-mediated CL to the total clearance. The free MMAE concentrations in cynomolgus monkeys following DCDT2980S administration were generally 10000 times lower than the concentration of DCDT2980S.

Cynomolgus monkeys were selected as the most relevant nonclinical species for the toxicology and PK/PD studies of DCDT2980S, given the comparable sequence homology of human and cynomolgus monkey CD22, similar binding affinity of DCDT2980S to human and cynomolgus monkey CD22, and comparable tissue cross-reactivity in both human and cynomolgus monkey tissues. DCDT2980S was well tolerated at doses of up to 3 mg/kg (highest non-severely toxic dose [HNSTD]) in monkeys, and up to or greater than 10 mg/kg in rats (severely toxic dose to 10% of rats [STD_{10}] $\geq$ 10 mg/kg). Reversible bone marrow toxicity and associated hematopoietic changes were observed in both rats and monkeys treated with DCDT2980S or MMAE, suggesting that the toxicity of DCDT2980S is related to MMAE. Additional effects on liver and lung in rats were minimal in severity and reversible, and did not occur in cynomolgus monkeys, which may be due to differences in species sensitivity, exposure, and/or pharmacokinetics.

Complete details of preclinical studies of DCDT2980S can be found in the DCDT2980S Investigator's Brochure.

1.2.1.2 DCDT2980S Clinical Data

a. Patient Enrollment

Both DCDT2980S monotherapy and combination therapy with rituximab have been studied in a Phase I study (DCT4862g) of patients with relapsed or refractory B-cell malignancies expected to express CD22, including indolent NHL, DLBCL, mantle cell lymphoma (MCL), and CLL.

All data presented herein is based on a data entry cutoff of *22 February 2013*, *with clinical data available* from *65* patients with NHL *(excluding patients with CLL)* enrolled in dose-escalation and expansion cohorts. These include *49* patients who were treated with single-agent DCDT2980S at doses ranging from 0.1 to 3.2 mg/kg administered intravenously every 21 days, and *16* patients who were enrolled into two Phase Ib cohorts with DCDT2980S administered at doses of 1.8 mg/kg (5 patients) and 2.4 mg/kg (*11* patients) in combination with 375 mg/m^2 rituximab.

Enrollment into CLL dose escalation cohorts *was closed on 31 May 2013*. Refer to the DCDT2980S Investigator Brochure for details regarding clinical data in CLL patients.

b. Pharmacokinetics

The pharmacokinetics of DCDT2980S have been characterized in the Phase I Study DCT4862g. DCDT2980S was administered to patients with NHL at dose levels ranging

from 0.1 to 3.2 mg/kg every-3-weeks (q3w). Three analytes were quantified: antibody-conjugated MMAE (acMMAE), total antibody, and free MMAE.

Preliminary pharmacokinetic analysis based on available data *as of 22 June 2012* is summarized below.

The mean value of CL estimates of acMMAE and total antibody of each dose level for doses of ≥ 1.0 mg/kg ranged from 17.6 to 21.3 mL/day/kg and from 10.5 to 16.2 mL/day/kg, respectively. Similar CL estimates for doses ≥ 1.0 mg/kg suggested dose proportional increase of acMMAE and total antibody exposure. CL estimates appeared to be slightly higher at doses < 1.0 mg/kg (0.1, 0.25, and 0.5 mg/kg), although data from these dose levels is limited. The CL of acMMAE was faster than total antibody at each dose level.

In patients with NHL, the mean value of the volume of distribution (V_{ss}) of acMMAE and total antibody of each dose level ranged from 69.2 to 130 mL/kg and from 97.4 to 154 mL/kg, respectively, across the dose levels tested, approximating human serum volume. V_{ss} values did not appear to change substantially with dose. The half-life for acMMAE and total antibody ranged from 2.9 to 7.0 days and from 4.4 to 13 days, respectively.

For acMMAE and total antibody, the time to maximum concentration occurred immediately after infusion. For free MMAE, the time to maximum concentration was approximately 2 to 3 days after infusion. C_{max} and AUC_{inf} of free MMAE appeared to increase with dose across the dose levels tested. A half-life of 3–4 days for free MMAE was observed, which is relatively long and similar to its parent conjugate, suggesting formation rate limited kinetics of free MMAE. No accumulation of free MMAE is expected for the q3w regimen. The C_{max} values of free MMAE in NHL patients were at least 100-fold lower compared to acMMAE concentrations at each dose level, suggesting a slow release of free MMAE from acMMME and potentially fast elimination once it is formed.

Preliminary comparisons of PK between patients with NHL and CLL (for which patients are enrolled into separate dose-escalation cohorts) treated with identical doses of DCDT2980S provide some insight into the factors that affect PK. Both acMMAE and total antibody were cleared faster in CLL patients than in NHL patients. This observation is likely to be related to the high number of circulating B cells generally observed in CLL patients, which may result in significant target-mediated clearance of DCDT2980S. The free MMAE exposure in CLL patients was relatively low compared to its parent conjugate.

The exposure parameters (C_{max} and AUC_{inf}) of total antibody, acMMAE and free MMAE were similar between DCDT2980S and DCDT2980S + rituximab at doses of 1.8 and 2.4 mg/kg, based on preliminary data. This observation suggests that, when given in

combination, rituxumab does not impact the PK of DCDT2980S; the effect of DCDT2980S on rituximab PK will be assessed.

All observations will be verified with additional data from the ongoing Phase I study as well as this study.

Refer to the DCDT2980S Investigator Brochure for complete and updated details.

c. Safety

Dose Limiting Toxicity

Study DCT4862g utilizes a standard 3+3 dose-escalation cohort enrollment scheme. Patients enrolled into each dose-escalation cohort in Study DCT4862g have been observed for dose-limiting toxicities (DLT) for a minimum of 21 days after their first dose of DCDT2980S. Any patient who did not complete the DLT observation period for any reason other than a DLT was replaced.

Separate dose-escalation cohorts enrolled patients with B-cell NHL and CLL. For the NHL dose escalation, DLTs of Grade 4 neutropenia occurred in 1 patient out of 3 DLT-evaluable patients in the 3.2 mg/kg single agent cohort and 1 patient out of *11* DLT-evaluable patients in the 2.4 mg/kg + rituximab cohort. Consequently, DCDT2980S at 2.4 mg/kg was determined to be the recommended Phase II dose (RP2D) as both monotherapy and in combination with rituximab.

For the CLL dose-escalation cohorts, one DLT was reported *to date*. This Grade 5 event of febrile neutropenia resulted in the patient's death. While the contribution of the study drug to the neutropenia could not be completely ruled out, other factors, including bone marrow involvement of disease that resulted in baseline anemia, thrombocytopenia and neutropenia, and clinical evidence of disease progression may have also played a contributory role.

Single-Agent DCDT2980S *and DCDT2980S Combined with Rituximab in NHL*

Forty-nine patients received single-agent DCDT2980S at a starting dose of ≥ 1.8 mg/kg (7 at 1.8 mg/kg, 42 at 2.4 mg/kg); 16 patients received DCDT2980S at a starting dose of ≥ 1.8 mg/kg in combination with rituximab (5 at 1.8 mg/kg, 11 at 2.4 mg/kg). Overall the safety profile of DCDT2980S combined with rituximab did not differ from that of single-agent DCDT2980S.

Treatment emergent hematologic and commonly reported nonhematologic adverse events for all grades in patients treated with single-agent DCDT2980S and DCDT2980S plus rituximab included neutropenia (29%), febrile neutropenia (3%), infection (system organ class; 43%), anemia (25%), thrombocytopenia (12%), peripheral neuropathy (28%), diarrhea (40%), pyrexia (14%), nausea (34%), and fatigue (55%). Treatment emergent Grade ≥ 3 adverse events included neutropenia (25%), febrile neutropenia (3%), infection (system organ class; 11%), anemia (5%),

peripheral neuropathy (3%), diarrhea (5%), pyrexia (2%), and fatigue (3%). Serious adverse events assessed by the treating investigator to be related to DCDT2980S were reported in 21% of patients. Dose discontinuations for adverse events were reported in 20% of patients.

Refer to the DCDT2980S Investigator's Brochure for complete and updated details related to safety.

d. Efficacy *in Non-Hodgkin's Lymphoma*

Investigator-based objective responses were observed in 17 of 43 (40%) patients treated with single-agent DCDT2980S and 5 of 15 (33%) patients treated with DCDT2980S combined with rituximab. Among patients with relapsed/refractory DLBCL, 11 of 28 (39%) objective responses (5 complete responses [CR] and 6 partial responses [PR]) were observed with single-agent DCDT2980S and 3 of 7 (43%; 2 CR, 1 PR) with DCDT2980S combined with rituximab. Among patients with relapsed/refractory indolent (iNHL), 6 of 13 (46%) objective responses (2 CR, 4 PR) were observed with single-agent DCDT2980S and 1 of 4 (PR) with DCDT2980S combined with rituximab.

Refer to the DCDT2980S Investigator Brochure for complete and updated details *related to* anti-tumor activity.

1.2.2 DCDS4501A

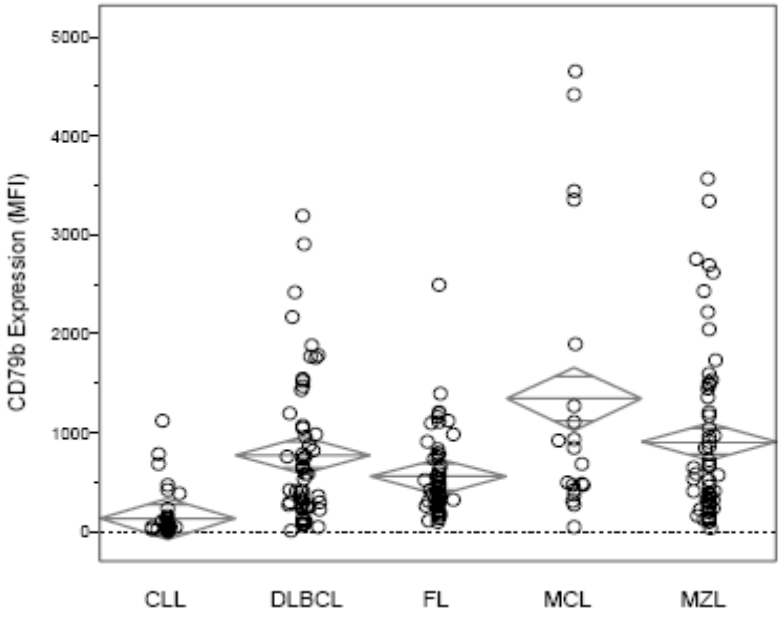
1.2.2.1 Background and Preclinical Data

CD79b is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of B-cell–derived malignancies, including nearly all NHL and CLL samples tested (see Figure 2) (Dornan et al. 2009). Antibodies bound to CD79b are rapidly internalized, making CD79b ideally suited for targeted delivery of cytotoxic agents (Polson 2007; 2009).

Similar to DCDT2980S, DCDS4501A is an ADC that contains a humanized immunoglobulin-G1 (IgG1) anti–human CD79b monoclonal antibody (MCDS4409A) and MMAE linked through MC-VC-PABC.

Comprehensive pharmacologic, PK, PD, and toxicological evaluations were undertaken to support the entry of DCDS4501A into clinical trials. Because DCDS4501A specifically recognizes CD79b on B cells of human but not on those of cynomolgus monkey, rat, or mouse, a surrogate ADC (DCDS5017A) that binds to cynomolgus monkey CD79b was generated to assess the antigen-dependent pharmacological, toxicological and pharmacokinetic/pharmacodynamic activities in cynomolgus monkeys. The structure, binding epitope, and binding affinity of the surrogate ADC are similar to DCDS4501A.

Figure 2 CD79b Expression Levels on B-Cell Tumor Cells



CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma.
CD79b expression levels (MFI, mean fluorescence intensity) on B-cell tumor cells were assessed by flow cytometry in patients diagnosed with the following B-cell lymphomas: CLL (n = 49), DLBCL (n = 59), FL (n = 58), MCL (n = 20), and MZL (n = 60).

DCDS4501A bound human CD79b with high affinity ($K_d = 1.83 \pm 0.26$ nM); the surrogate ADC also showed similar high binding affinity to cynomolgus monkey CD79b. DCDS4501A displayed potent and selective inhibition of tumor cell proliferation in vitro ($IC_{50} = 0.071$ nM $\pm$ 0.01 nM) in cell viability assays. Moderate ADCC but no CDC activity was observed with the unconjugated clinical candidate antibody MCDS4409A. Both clinical and surrogate unconjugated antibodies showed no appreciable cytokine release when evaluated in in vitro cytokine release assays with peripheral blood mononuclear cells (PBMCs). Moderate elevations in IL-1α and IP-10 were observed only with the unconjugated clinical antibody, however the clinical significance of these observations are not known since IL-1α and IP-10 are not produced by B-cells, are not involved in B-cell signaling through CD79b, and are not associated with cytokine-release syndromes in vivo.

Single intravenous (IV) doses of DCDS4501A resulted in inhibition of tumor growth in murine xenograft models of lymphoma. Tumor regression was observed at doses ranging from 0.5 to 3 mg/kg. In contrast, MCDS4409A showed no activity. DCDS4501A administered at 5 mg/kg demonstrated better anti-tumor activity compared to a current standard-of-care regimen (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) in xenograft models of NHL. PD studies demonstrated that at doses of the surrogate ADC ranging from 0.3 to 5 mg/kg resulted in a decrease of peripheral-blood B cells in cynomolgus monkeys. A preferential decrease of proliferating

B-cells (CD20+Ki67+) compared to the resting B cells (CD20+ Ki67−) by the surrogate ADC was demonstrated in cynomolgus monkeys, in line with the expected mechanism of action of an anti-mitotic agent, MMAE.

Due to B-cell-mediated CL, non-linear pharmacokinetics were observed with the surrogate ADC in cynomolgus monkeys following single IV doses of 0.3–3 mg/kg or four doses of 3 and 5 mg/kg given q3w. The total antibody exposure after the fourth dose increased approximately 1.2- to 1.5-fold compared to the first dose. As expected, the toxicokinetic profile of the clinical ADC in rats and cynomolgus monkeys was linear in the tested dose range. Consistent with the half-life of the clinical ADC, minimal accumulation was observed following weekly dosing in rats and no accumulation was observed following every-3-week dosing in cynomolgus monkeys. The free MMAE concentrations in plasma following administration of the clinical or surrogate ADCs were generally low and overall did not exceed 2 ng/mL, regardless of dose. The overall incidence of anti-therapeutic antibodies (ATAs) was 20%–67% following administration of the clinical or surrogate ADCs in cynomolgus monkeys; however, the ATAs did not appear to impact the toxicokinetic/pharmacokinetic parameter estimates.

In repeat-dose toxicity studies in rats and cynomolgus monkeys, DCDS4501A and the surrogate ADC were well tolerated in monkeys up to 5 mg/kg and 3 mg/kg respectively, with 3 mg/kg considered the highest non-severely toxic dose (HNSTD). In rats, DCDS4501A was well tolerated up to 6 mg/kg ($STD_{10} = 10$ mg/kg). The predominant antigen-independent findings associated with DCDS4501A or surrogate ADC exposure were reversible bone marrow toxicity and associated peripheral blood cell effects in both monkeys and rats. Administration of the surrogate ADC to monkeys also resulted in expected antigen-dependent reversible decreases in peripheral blood B cells and the disappearance of B-cell germinal centers in splenic lymphoid follicles at doses ≥ 3 mg/kg. Additional findings observed in rats but not in monkeys included thymic lymphoid depletion at ≥ 6 mg/kg, minimal to mild liver toxicities (at ≥ 6 mg/kg), lung toxicities at 10 mg/kg in male animals only, and a slight increase in apoptosis and mitoses in multiple tissues, including skin and adnexa. Hepatobiliary toxicity consisted of transient dose-dependent liver enzyme elevations accompanied by minimal to slight dose-dependent increases in mitotic figures/apoptosis in hepatocytes, sinusoidal cells, and bile duct epithelium as well as minimal to slight dose-dependent random focal hepatic necrosis. Pulmonary toxicity was characterized by minimal to slight dose-dependent alveolar macrophage infiltration, sometimes accompanied by minimal to slight type II pneumocyte hyperplasia/hypertrophy. These findings were consistent with the expected pharmacologic effect of MMAE on inducing mitotic arrest due to inhibition of tubulin polymerization. Except for two individual instances (one female given 10 mg/kg in the liver and one male given 10 mg/kg in the lung), these findings were completely reversible after a 6-week recovery period. Non-reversible male reproductive toxicity, characterized by degeneration of testicular seminiferous tubules, was observed in rats at all doses.

Complete details of preclinical studies of DCDS4501A can be found in the DCDS4501A Investigator's Brochure.

1.2.2.2 DCDS4501A Clinical Data

a. Patient Enrollment

Both DCDS4501A monotherapy and combination therapy with rituximab are being studied in a Phase I study (DCS4968g) of patients with relapsed or refractory B-cell malignancies expected to express CD79b, including indolent NHL, DLBCL, mantle cell lymphoma (MCL), and CLL.

All data presented herein is based on a data entry cutoff of *28 February 2013*, with clinical data available from *60* patients with NHL *(excluding patients with CLL)* enrolled in dose-escalation and expansion cohorts. These include *51* patients who were treated with single-agent DCDS4501A ranging from 0.1 to 2.4 mg/kg administered intravenously every 21 days, and *9* patients who were enrolled into a single Phase Ib cohort with DCDS4501A administered at a dose of 2.4 mg/kg in combination with 375 mg/m^2 rituximab.

In the CLL dose escalation cohorts, two DLTs were reported at the single-agent dose of 1.8 mg/kg. Enrollment into the CLL cohorts was stopped on 7 January 2013. Refer to the DCDS4501A Investigator Brochure for details regarding clinical data in CLL patients.

b. Pharmacokinetics

The pharmacokinetics of DCDS4501A were characterized in a Phase I study DCDS4501A. DCDS4501A was administered in patients with NHL at escalating doses of 0.1 to 2.4 mg/kg q3w as monotherapy and following administration of rituximab in the Phase Ib cohort. Three analytes were quantified: antibody-conjugated MMAE (acMMAE), total antibody, and free MMAE.

Preliminary pharmacokinetic analysis based on available data *as of 22 June 2012* is summarized below. The CL estimates of acMMAE and total antibody of each dose level is in the range of 14.9–21.2 mL/day/kg and 7.12 to 27.9 mL/day/kg, respectively. CL estimates were similar across doses of 0.1–2.4 mg/kg tested, suggesting dose proportional increase of acMMAE and total antibody exposure. The clearance of acMMAE was faster than total antibody at each dose level.

The mean value of the volume of distribution (V_{ss}) of acMMAE and total antibody of each dose level ranged from 61 to 80.8 mL/kg and from 59.4 to 114.3 mL/kg, respectively, across the dose levels tested, which approximated human serum volume. V_{ss} values did not appear to change substantially with dose. The half-lives for acMMAE and total antibody are from 2.4 to 5.5 days and 2.9 to 7 days, respectively.

In a single agent dose-escalation study, for acMMAE and total antibody, the time to maximum concentration occurred immediately after infusion. For free MMAE, the time to maximum concentration was approximately 2 to 3 days after infusion. C_{max} and AUC_{inf} of free MMAE appear increased with dose across the dose levels. A half-life of 3–4 days

for free MMAE was observed, which is relatively long and similar to acMMAE and suggests formation rate limited kinetics for free MMAE. No accumulation of free MMAE is expected for the q3w regimen. The C_{max} values of free MMAE in NHL patients were at least 100-fold lower compared to acMMAE concentrations at each dose level, suggesting a slow release of free MMAE from acMMAE and potentially fast elimination once it is formed.

Preliminary comparisons of PK between patients with NHL and CLL (for which patients are enrolled into separate dose-escalation cohorts) treated with identical doses of DCDS4501A provide some insight into the factors that affect PK. Both acMMAE and total antibody were cleared faster in CLL patients than in NHL patients. This observation is likely to be related to the high number of circulating B cells generally observed in CLL patients, which may result in significant target-mediated clearance of DCDS4501A. The free MMAE exposure in CLL patients was relatively low compared to its parent conjugate.

To date, PK data for patients treated with DCDS4501A in combination with rituximab is limited. Consequently, full comparison with single-agent DCDS4501A PK is not possible. Based on very limited data from 3 patients, total antibody PK was comparable between 2.4 mg/kg of DCDS4501A administered as single-agent and following rituximab administration, suggesting that when given in combination, rituximab does not affect the PK of DCDS4501A; the effect of DCDS4501A on rituximab PK will be assessed.

All observations will be verified with additional data from the ongoing Phase I study as well as this study.

Refer to the DCDS4501A Investigator Brochure for complete and updated details.

c. Safety

Dose-Limiting Toxicities

Study DCS4968g utilizes a standard 3+3 dose escalation cohort enrollment scheme. Patients enrolled into each dose-escalation cohort in Study DCS4968g have been observed for DLTs for a minimum of 21 days after their first dose of DCDS4501A. Any patient who did not complete the DLT observation period for any reason other than a DLT was replaced.

DLT of Grade 4 neutropenia occurred in 1 patient out of 10 DLT-evaluable patients in the 2.4 mg/kg single agent cohort and 1 patient out of 9 DLT-evaluable patients in the 2.4 mg/kg + rituximab cohort. Doses of DCDS4501A greater than 2.4 mg/kg as monotherapy or in combination with rituximab were not assessed. Consequently, DCDS4501A at 2.4 mg/kg was therefore determined to be the RP2D as both monotherapy and in combination with rituximab. Patients are currently being enrolled in monotherapy expansion cohorts for various types of NHL in order to collect and further characterize both single agent and combination safety data.

In the CLL dose-escalation cohorts, two DLTs were reported at the single-agent dose of 1.8 mg/kg. One patient had a Grade 4 neutropenia, and 1 patient had a Grade 4 invasive fungal infection.

Single-Agent DCDS4501A *and DCDS4501A Combined with Rituximab*

Fifty-one patients received single agent DCDS4501A at a starting dose of ≥ 1.8 mg/kg (6 at 1.8 mg/kg, 45 at 2.4 mg/kg); an additional 9 patients received DCDS4501A at a dose of 2.4 mg/kg in combination with rituximab. Overall, the safety profile of DCDS4501A combined with rituximab did not differ from that of single-agent DCDS4501A.

Treatment emergent hematologic and commonly reported non-hematologic adverse events for all grades in patients treated with single-agent DCDS4501A and DCDS4501A plus rituximab included neutropenia (50%), febrile neutropenia (5%), infection (system organ class; 35%), anemia (13%), thrombocytopenia (18%), peripheral neuropathy (32%), diarrhea (43%), pyrexia (37%), nausea (35%), and fatigue (18%). Treatment emergent Grade ≥ 3 adverse events included neutropenia (43%), febrile neutropenia (5%), infection (system organ class; 10%), anemia (8%), peripheral neuropathy (7%), diarrhea (3%), pyrexia (2%), and fatigue (5%). Serious adverse events assessed by the treating investigator to be related to DCDS4501A were reported in 20% of patients. Dose discontinuations for adverse events were reported in 33% of patients.

Refer to the DCDS4501A Investigator's Brochure for complete and updated details related to safety.

d. Efficacy

Investigator-based objective responses were observed in 28 of 49 (57%) patients treated with single-agent DCDS4501A and 7 of 9 patients (78%) treated with DCDS4501A combined with rituximab. Among patients with relapsed/refractory DLBCL, objective responses were observed in 16 of 30 (53%; 4 CR, 12 PR) patients treated with DCDS4501A; 1 patient with DLBCL was treated with DCDS4501A combined with rituximab and achieved a PR. Among patients with relapsed/refractory iNHL, objective responses were observed in 7 of 14 (50%; 2 CR, 5 PR) patients treated with single-agent DCDS4501A and 5 of 5 (100%; 2 CR, 3 PR) patients treated with DCDS4501A plus rituximab.

Refer to the DCDS4501A Investigator Brochure for complete and updated details regarding anti-tumor activity.

1.2.3 Rituximab

Rituximab has been shown to be an effective treatment for CD20-positive B-cell malignancies and is commonly used both as a single agent and in combination with cytotoxic chemotherapy. Rituximab binds to CD20, a hydrophobic, transmembrane

protein that is present on pre–B and mature B cells and in > 90% of B-cell NHLs. It exerts its cytotoxic effects via complement-mediated B-cell lysis, ADCC, and induction of apoptosis (Cartron et al. 2004).

In the United States, rituximab has been approved by the U.S. Food and Drug Administration (FDA) for the following indications in NHL: as a single agent for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL; for the treatment of relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL, including initial treatment weekly for eight doses and re-treatment (weekly for four doses) in patients who responded to an initial course of rituximab; for the treatment of low-grade, CD20-positive B-cell NHL, in combination with cyclophosphamide, vincristine, and prednisone (CVP) induction chemotherapy in previously untreated patients with follicular, CD20-positive NHL; as treatment in previously untreated patients with low-grade, CD20-positive NHL who achieve an objective response or stable disease (SD) following CVP induction; as maintenance therapy for previously untreated follicular CD20-positive B-cell NHL after achieving a response to a regimen including chemotherapy and rituximab.

In the European Union, rituximab (MabThera®) is approved for the treatment of the following indications in NHL: treatment of patients with Stage III–IV follicular NHL who are chemotherapy-resistant or in their second or subsequent relapse after chemotherapy; treatment of patients with CD20-positive DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy; as front-line therapy in Stage III–IV follicular NHL in combination with CVP chemotherapy; as maintenance therapy in patients with relapsed or refractory, follicular NHL responding to induction treatment with CHOP or rituximab + CHOP; and as maintenance treatment for patients with follicular lymphoma who have responded to initial treatment with rituximab plus chemotherapy.

Rituximab has also been approved for the treatment of CLL. The European Medicines Agency (EMA) granted an approval for the use of rituximab in combination with chemotherapy for previously untreated CLL. The FDA approved the use of rituximab in combination with fludarabine and cyclophosphamide for patients with previously untreated and previously treated CD20-positive CLL.

Refer to the Rituximab Product Insert/Summary of Product Characteristics for complete details regarding clinical data related to approved indications. For rituximab safety information, refer to local rituximab prescribing information.

1.3 RATIONALE FOR DOING THIS STUDY

The goals of this Phase II study are to continue to assess the safety, tolerability, and biologic and clinical activity of the combinations of DCDT2980S and rituximab and DCDS4501A and rituximab in two specific NHL patient populations: patients with relapsed or refractory follicular NHL, and patients with relapsed or refractory DLBCL.

These patients continue to have an extremely poor prognosis with no curative options available. Consequently new therapeutic options are needed.

DCDT2980S, DCDS4501A and rituximab each target antigens specific to B-cell malignancies including follicular NHL and DLBCL (see Figures 1 and 2).

The Phase II study design permits an assessment of the clinical benefit provided by each of these molecules in combination with rituximab, which has established clinical activity in B-cell malignancies both as monotherapy and in combination with chemotherapy. Data from this study will help inform the feasibility of the combination regimens in earlier lines of therapy (e.g., as first-line therapy in newly diagnosed patients).

The feasibility of combining an ADC with rituximab has previously been tested clinically with the combination of another, different CD22-specific ADC, inotuzumab ozogamicin (CMC-544), with results suggesting that the addition of rituximab may have increased clinical activity without significant increase in toxicity over the ADC alone in patients with aggressive NHL (Luis et al. 2006; Nam et al. 2009; Nina et al. 2010). As noted in Sections 1.2.1 and 1.2.2, the combinations of DCDT2980S and rituximab, and DCDS4501A and rituximab have been shown to have acceptable safety in patients with relapsed or refractory NHL in the Phase I studies (DCT4862g and DCS4968g).

Given the relatively poor prognosis of patients with relapsed or refractory hematologic malignancies that have failed standard therapies and the nonclinical toxicity profile associated with DCDT2980S and DCDS4501A treatment, and the clinical safety profile observed to date for both ADCs, the risk-benefit ratio of a clinical study of DCDT2980S and DCDS4501A, each combined with rituximab, is considered acceptable.

1.3.1 *Rationale for Assessing ADC Dose of 1.8 mg/kg Combined with Rituximab in iNHL*

Based on available Phase I data (see Section 1.2.1 and 1.2.2), both DCDT2980S and DCDS4501A as single-agents and combined with rituximab have shown early signs of clinical activity in heavily pretreated patients with relapsed/refractory NHL. However, early evidence in the Phase I studies indicate that duration of study treatment may be limited by tolerability to ADC. Specifically, for both ADCs, peripheral sensory neuropathy has been identified as a known risk (see Section 3.4.2). Notably, 4 of 7 and 5 of 11 discontinuations for adverse events in Studies DCT4862g and DCS4968g, respectively, were the result of peripheral neuropathy.

Because of the chronic course and incurability of iNHL, treatment paradigms are increasingly emphasizing tolerability to treatment in addition to efficacy. As both DCDT2980S and DCDS4501A have shown single-agent activity at the 1.8 mg/kg dose level (Advani et al. 2012; Palanca-Wessels et al. 2012), the purpose of enrolling additional cohorts of patients with follicular lymphoma is to determine whether lower

doses of ADC in combination with standard doses of rituximab result in improved tolerability while maintaining efficacy in follicular lymphoma.

In contrast to iNHL, treatment paradigms in relapsed/refractory aggressive lymphomas such as DLBCL continue to place a premium on anti-tumor activity and higher tolerance for treatment-related toxicity given that durations of disease control and survival are substantially shorter and that treatment options are extremely limited. Early Phase I data suggest lower rates of study treatment discontinuation for adverse events among patients with DLBCL compared with patients with iNHL. Taken together with anti-tumor activity observed to date, the risk-benefit profile of the currently tested ADC dose of 2.4 mg/kg is considered acceptable

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objectives of this study are the following:

- To assess the safety and tolerability of the combination of DCDT2980S and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the safety and tolerability of the combination of DCDS4501A and rituximab administered to patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDT2980S and rituximab in patients with relapsed or refractory follicular NHL and DLBCL
- To assess the anti-tumor activity of the combination of DCDS4501A and rituximab in patients with relapsed or refractory follicular NHL and DLBCL

2.2 SECONDARY OBJECTIVES

2.2.1 Safety Objectives

The secondary safety objectives of this study are the following:

- To assess the incidence of antibody formation to DCDT2980S and DCDS4501A
- To compare the safety and tolerability of the combination of DCT2980S and rituximab and DCDS4501A and rituximab

2.2.2 Activity Objective

The secondary activity objective of the study is the following:

- To compare the anti-tumor activity of the combination of DCT2980S and rituximab and DCDS4501A and rituximab

2.2.3 Pharmacokinetic Objectives

The PK objectives of this study are the following:

- To characterize the pharmacokinetics of DCDT2980S and rituximab in patients with relapsed or refractory NHL when the two drugs are given in combination
- To characterize the pharmacokinetics of DCDS4501A and rituximab in patients with relapsed or refractory NHL when the two drugs are given in combination

2.3 EXPLORATORY OBJECTIVES

2.3.1 Biomarker Objectives

The objectives of this study related to assessment of biologic markers are the following:

- To make a preliminary assessment of biologic markers that might act as predictors of DCDT2980S + rituximab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL
- To make a preliminary assessment of biologic markers that might act as predictors of DCDS4501A + rituximab combination anti-tumor activity and allow assessment of response in different prognostic subgroups of DLBCL and follicular NHL

2.3.2 Patient Quality of Life Objective

The objective of this study related to assessment of patient quality of life is the following:

- To assess patient tolerability to study treatment and the impact of study treatment on patient quality of life based on patient reported outcomes (PRO)

2.3.3 Crossover Treatment Objective

The objective of this study related to assessment of crossover treatment is the following:

- To preliminarily assess the safety and tolerability and anti-tumor activity of DCDT2980S and DCDS4501A, either as a single-agent or in combination with rituximab, as crossover treatment following disease progression on initial study treatment *(Note: This objective only applies to patients enrolled in Arms A and B [see Section 3.1])*

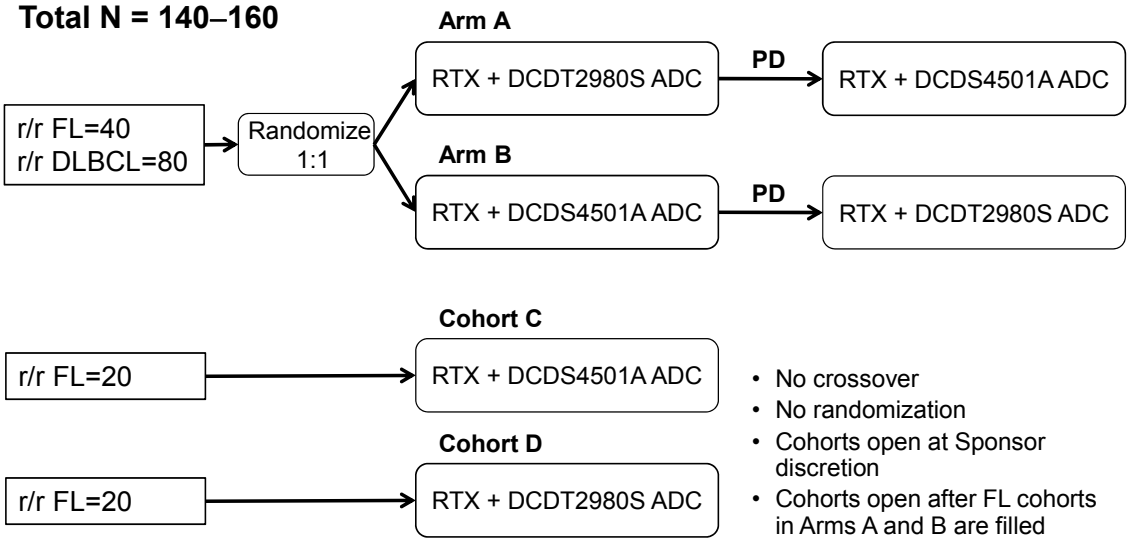
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, multicenter, open-label study. A total of approximately *140–160* patients (approximately *60–80* patients with relapsed or refractory follicular NHL and approximately 80 patients with relapsed/refractory DLBCL) will be enrolled at approximately 30–40 investigative sites worldwide. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

The study will be composed of a randomized portion and a nonrandomized portion, as illustrated in Figure 3.

Figure 3 Study Schema



Arms A and B: RTX (375 mg/m^2) + ADC (2.4 mg/kg) administered in every-21-day cycles.
Cohorts C and D: RTX (375 mg/m^2) + ADC (1.8 mg/kg) administered in every-21-day cycles.

DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; PD=progressive disease; r/r=relapsed or refractory; RTX=rituximab.

3.1.1 *Randomized Portion of the Study (Arms A and B)*

Following determination of eligibility, patients within each disease group will be randomized in a 1:1 ratio to receive one of two treatments:

- Arm A: Rituximab (375 mg/m^2) followed by DCDT2980S (2.4 mg/kg) every 21 days;
- Arm B: Rituximab (375 mg/m^2) followed by DCDS4501A (2.4 mg/kg) every 21 days

The first day of treatment constitutes Day 1 of each cycle. A typical cycle is 21 days in duration.

A dynamic hierarchical randomization scheme will be employed with respect to the following stratification factors:

- For patients with follicular lymphoma (see Section 3.1.1 for definitions)

  Rituximab refractory disease (no response or disease relapse < 6 months from last rituximab treatment) vs. rituximab relapsed disease (disease relapse after response ≥ 6 months from last rituximab treatment)

- For patients with DLBCL (see Section 3.1.2 for definitions)

  Second-line vs. third-line (or beyond) therapy

  For second-line patients, disease relapse or no objective response (CR, unconfirmed CR [Cru], or PR) <12 months from the start of initial therapy versus disease relapse, after initial objective response (CR, CRu or PR), ≥12 months from start of initial therapy

  For third-line patients, failure to achieve a CR or progression < 6 months of start of most recent therapy versus CR or progression ≥ 6 months from start of most recent therapy

No formal testing comparing the two treatment arms in the randomized portion of the study is planned.

3.1.2 *Nonrandomized Portion of the Study (Cohorts C and D)*

Only select investigator sites that have agreed to participate in the nonrandomized portion of the study will enroll patients into these cohorts.

Patients with relapsed or refractory follicular NHL will be enrolled in Cohorts C and D to receive rituximab (375 mg/m^2) combined with DCDT2980S or DCDS4501A at a dose of 1.8 mg/kg. The first day of treatment constitutes Day 1 of each cycle. A typical cycle will be 21 days in duration.

The opening of either or both cohorts will be at the Sponsor's discretion and only after the enrollment of follicular lymphoma patients into the randomized portion of the study is completed. Patients will not be randomized to receive one treatment or the other. It is anticipated that Cohort C and D will be opened sequentially.

3.1.3 *All Patients*

All patients, regardless of assigned arm/cohort will receive DCDT2980S or DCDS4501A and rituximab administered by IV infusion on a 21-day cycle. For the first two cycles, rituximab will be administered by IV infusion on Day 1 and DCDT2980S or DCDS4501A will be administered by IV infusion on Day 2. In the absence of any infusion-related adverse events, rituximab and DCDT2980S or DCDS4501A may be administered on the same day (Day 1) in subsequent cycles beginning with the third cycle. In this instance, rituximab will be administered first, followed by DCDT2980S or DCDS4501A. In certain circumstances, e.g., infusion-related reactions requiring interruption or slowing of infusion rate, rituximab may be administered over 2 days, e.g., Day 1 and Day 2 of the cycle; in this case, DCDT2980S or DCDS4501A may be administered on Day 2 following completion of the rituximab infusion or on Day 3 of the cycle.

Patients may receive treatments for up to 1 year (17 cycles on an every-21-day schedule) if not discontinued due to significant toxicity, disease progression, or withdrawal from study.

Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in Appendices A-1, A-2, and A-3. Initial response assessments in this study will be performed every 3 months from the initiation of therapy until study treatment completion or early termination (e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment). Additional response assessments for patients who proceed to crossover treatment (see Section 3.1.3) will be performed as described in Appendix A-2; response assessments for patients who discontinue study treatment (both initially assigned treatment and crossover treatment) for reasons other than disease progression will be performed as described in Appendix A-3.

Responses to study treatment will be based on investigator assessments. In addition, tumor assessment data will be transmitted to an Independent Review Facility (IRF) for collection and possible independent review.

3.1.4 Follicular NHL Cohort

Patients with relapsed or refractory follicular NHL will be enrolled into the study as defined by the following:

- Relapsed to regimens containing rituximab, defined as documented history of response (CR, CRu, or PR) of $\geq$6 months in duration from completion of all prior rituximab-containing regimens. A rituximab-containing regimen is defined as rituximab as a single agent during induction and/or maintenance, or in combination with other agents during induction and/or maintenance.
- Refractory to any prior regimen containing rituximab, defined as no response to, or progression within 6 months of completion of, the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:

  Patients with progressive disease while receiving rituximab monotherapy, rituximab combined with chemotherapy, or rituximab maintenance therapy; patients must have received at least one full dose (375 mg/m^2) of rituximab

  Patients with no objective response (PR or CR) to a rituximab-containing regimen consisting of at least 4 weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

  Patients with disease relapse, after having achieved an objective response, within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least 4 cycles of rituximab combined with chemotherapy

Enrollment of patients with refractory disease as defined above may be limited to no greater than 60% of the total follicular NHL cohort, in order to avoid overrepresentation of the refractory disease population.

3.1.5 DLBCL Cohort

Patients with relapsed or refractory DLBCL who are determined by the investigator to be ineligible for high dose therapy with autologous stem cell rescue/stem cell transplant (SCT) as determined by the investigator will be enrolled into the study as defined by the following:

- Second-line SCT-ineligible patients with progressive disease or no response (SD) $<$ 12 months from start of initial therapy (2L refractory)
- Second-line SCT-ineligible patients with disease relapse after initial response $\geq$ 12 months from start of initial therapy (2L relapsed)
- Third-line (or beyond) SCT-ineligible patients with progressive disease or no response (SD) $<$ 6 months from start of prior therapy (3L + refractory)
- Third-line (or beyond) SCT-ineligible patients with disease relapse after initial response $\geq$ 6 months from start of prior therapy (3L+ relapsed)

Enrollment to any of the above four categories may be limited to no greater than 40% of the DLBCL cohort—and to no more than 60% of the two refractory categories combined—in order to avoid overrepresentation of any specific subpopulation, refractory patients in particular.

3.1.6 Crossover Treatment *(Randomized Patients Only)*

Patients *randomized* to Arm A or Arm B who develop progressive disease may be eligible to receive crossover treatment consisting of rituximab and the other ADC, or the other ADC alone, e.g., Arm B treatment for patients who have disease progression while receiving Arm A treatment and vice versa, provided the following conditions are met:

- Patients must not have experienced a toxicity requiring the discontinuation of DCDT2980S/DCDS4501A treatment OR experienced toxicity during the last dose of study treatment that would preclude treatment with the crossover regimen.

  Patients who had modifications to dosing and/or schedule on the initial study treatment will be permitted to receive crossover treatment in the absence of toxicities on the modified dose and/or schedule. The dose and schedule of crossover treatment will be determined by the investigator and the Medical Monitor.

  Patients who had rituximab discontinued and continued on single-agent DCDT2980S/DCDS4501A treatment may receive crossover treatment of single-agent DCDS4501A/ DCDT2980S

- Patients must have radiographically documented disease progression
- Patients must meet all inclusion and exclusion criteria described in Sections 4.1.1 and 4.1.2, except for those related to prior rituximab treatment.

- Acceptable toxicity: All study drug–related adverse events from the initial study treatment must have decreased to Grade 1 or baseline grade on or before the first day of treatment on the crossover regimen. Exceptions may be allowed after a careful assessment and discussion of the risk-benefit balance with the patient by the investigator and approval from the Medical Monitor.
- Administration of crossover treatment must be in the best interests of the patient as determined after a careful assessment and discussion of risk-benefit balance with the patient by the investigator and approval from the Medical Monitor.
- A tumor biopsy (see Section 4.5.1.9) will be required for patients with safely accessible site of disease, defined as requiring only local anesthesia and in general excluding brain, lungs or any internal organs that may subject patients to significant risk.

  Patients for whom a safely accessible site of disease is not present may still receive crossover treatment without undergoing a biopsy. Eligibility to receive crossover treatment should be discussed with and approved by the Medical Monitor.

  A tumor biopsy of a safely accessible site of disease is optional for patients who are not eligible for study cross over.

Patients who are determined to be eligible for study crossover will be treated as follows:

- Assessments obtained at the initial study treatment discontinuation visit (see Section 4.5.4) may be used as screening assessments for crossover treatment. The following re-screening assessments must be repeated/obtained within 1 week prior to starting treatment on the crossover regimen in order to re-establish baseline pretreatment clinical and disease status: targeted physical exam, ECOG status and hematology and serum chemistry laboratories.

  Re-screening tests for Hepatitis B and C do not need to be performed unless there is clinical suspicion of Hepatitis B and/or C positivity.

  A radiographic tumor assessment must also be performed, unless already done to document disease progression, within 6 weeks prior to starting crossover treatment.
- Crossover treatment will begin no later than 42 days after the last dose of the prior study treatment.

Patients will be treated with the crossover treatment until a second disease progression event relative to the tumor assessment documenting progressive disease on the initial study treatment, clinical deterioration and/or intolerance to the crossover treatment for up to a maximum of 1 year (17 cycles on an every-21-day schedule). Patients will be evaluated for safety and efficacy according to the schedules of assessments outlined in Appendices A-2. Response assessments for patients who discontinue study treatment for reasons other than disease progression will be performed as described in Appendix A-3.

Clinical data and exploratory data derived from tumor biopsies obtained prior to crossover treatment will be monitored on an ongoing basis. Genentech has the right to restrict or suspend enrollment into crossover treatment at any time. Reasons for this may include, but are not limited to, the following:

- The incidence or severity of adverse events during crossover treatment indicates a potential safety hazard to patients.
- Patient enrollment into crossover treatment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- *Patients who are enrolled into the nonrandomized portion of the study (Cohorts C and D) will not have the option to receive crossover treatment upon disease progression (see Section 3.2 for rationale).*

3.2 RATIONALE FOR STUDY DESIGN

The primary rationale for *the* randomized non-comparative *portion of the study* is to assess clinical activity for the ADCs DCDT2980S and DCDS4501A in patients with relapsed/refractory NHL. The study design ensures that the patient populations under study are balanced with respect to critical variables such as prior therapy and ensures consistent clinical assessment of safety and efficacy. The collection and assessment of tumor tissue obtained prior to first study treatment and following progressive disease will provide further understanding of disease biology, possible mechanisms of resistance to the study treatment and initial insights into tumor subtypes based on tumor biomarkers that are sensitive to study treatment. Finally, the inclusion of study treatment crossover (see Section 3.1.3) will address important questions regarding efficacy and tolerability of a second ADC-rituximab combination following disease progression on the initial ADC-rituximab combination.

The primary rationale for the nonrandomized portion of the study is to assess the therapeutic index (i.e., the balance of efficacy and tolerability of DCDT2980S and DCDS4501A at a dose of 1.8 mg/kg in patients with relapsed or refractory follicular NHL). An informal comparison between patients with follicular NHL treated at the two doses of the ADC will help determine if tolerability is improved at the lower ADC dose without substantial compromise of efficacy.

The clinical feasibility of an ADC-rituximab combination regimen in patients with relapsed/refractory NHL has been previously studied. Results from studies of rituximab in combination with a different CD22-specific ADC, inotuzumab ozogamicin, demonstrated that when combined with rituximab the ADC was able to be given at the single-agent MTD without the need for dose reduction of the ADC due to the lack of significant overlapping toxicity (Luis et al. 2006; Nam et al. 2009; Nina et al. 2010).

DCDT2980S and DCDS4501A are both being evaluated as single agents and in combination with rituximab in ongoing Phase I studies DCT4862g and DCS4968g, respectively. Results from these ongoing Phase I trials have determined an MTD of

2.4 mg/kg for single-agent DCDT2980S and the RP2D of 2.4 mg/kg for single-agent DCDS4501A in patients with mixed NHL. In addition, the RP2D of DCT2980S and DCDS4501 each in combination with rituximab (375 mg/m^2) on an every-21-day schedule was determined to be 2.4 mg/kg. Study GO27834 will continue to assess the cumulative safety and longer-term tolerability of ADC-rituximab combination therapy.

Study drug dosing will occur on Days 1 and 2 of each 21-day (or 28-day) cycle to allow for recovery from potential bone marrow toxicity.

3.2.1 Rationale for the PK sample schedule

PK data obtained in this study will be important in informing potential future trials with this combination. Given the likely changing effect of peripheral B-cell counts, tumor burden, and target antigen expression on target-mediated drug clearance over multiple doses of DCDT2980S or DCDS4501A plus rituximab when the two drugs are given in combination, the drug levels of DCDT2980S or DCDS4501A-related analytes and rituximab will be assessed in this combination study.

In Studies DCT4862g and DCS4968g, single-agent DCDT2980S and DCDS4501A administered by IV infusion every 21 days was evaluated at doses ranging from 0.1 to 3.2 mg/kg for DCDT2980S, and 0.1 mg/kg to 2.4 mg/kg for DCDS4501A, in patients with NHL. Intensive PK sampling of all patients in the ongoing Phase I studies will provide sufficient data to allow complete profiling of the distribution and elimination phases for DCDT2980S and DCDS4501A and the investigation of potential correlations between various PK parameters and efficacy and/or toxicity. Consequently a reduced PK sampling scheme of DCDT2980S and DCDS4501A will be used in this Phase II study.

The PK data collected in this Phase II study will allow further characterization of the PK properties of DCDT2980S and DCDS4501A. In addition, the DCDT2980S and DCDS4501A concentration results from this study will be compared with available data from the single-agent clinical studies to evaluate whether concurrent administration of rituximab affects the exposure of DCDT2980S and/or DCDS4501A.

Rituximab serum concentration measurements from this study will be compared with PK data from historical rituximab clinical studies to evaluate whether the combination with DCDT2980S and/or DCDS4501A affects the PK of rituximab.

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety and tolerability of the combination of DCDT2980S and rituximab and DCDS4501A and rituximab will be assessed using the following safety outcome measures:

- Incidence, nature, and severity of adverse events
- Incidence of anti-DCDT2980S or anti-DCDS4501A antibodies

- Changes in vital signs
- Changes in laboratory values

3.3.2 Pharmacokinetic/Pharmacodynamic Outcome Measures

The following PK parameters will be derived from the serum concentration–time profiles of total antibody (the sum of conjugated and unconjugated antibody), including rituximab, and plasma concentration-time profiles of antibody conjugated-MMAE (acMMAE) and free MMAE following administration of DCDT2980S or DCDS4501A, when appropriate as data allow:

- Total exposure (area under the concentration-time curve [AUC])
- Maximum plasma and serum concentration (C_{max})
- Clearance (CL)
- Terminal half-life ($t_{1/2}$)
- Steady state volume of distribution (V_{ss}).

Compartmental, non-compartmental, and/or population methods may be used. Other parameters, such as accumulation ratio and trough plasma and serum concentration (C_{min}), may also be calculated.

The following PD outcome measures will be assessed when appropriate, as data allow:

- Peripheral blood B-cell depletion and recovery. For each visit at which $CD19^+$ B-cell measurements are taken, B-cell data will be listed for each patient by dose level as follows:

  Absolute blood cell counts

  Percent change relative to the baseline blood counts

  $CD19^+$ B-cell recovery, defined as the timepoint when the values return to baseline levels or $\geq$ 50% of baseline levels

3.3.3 Activity Outcome Measures

The following activity outcome measures will be assessed:

- Objective response, defined as a PR or CR
- Duration of objective response, defined as the first occurrence of a documented objective response until the time of relapse or death from any cause
- Progression-free survival (PFS), defined as the date of randomization to the first occurrence of progression or death within 30 days of the last administration of study drug, whichever occurs first
- Overall survival (OS), defined as the time from the date of randomization to the date of death from any cause

Objective response and disease progression will be determined using standard criteria for NHL (Cheson et al. 2007; see Appendix C).

3.3.4 Exploratory Outcome Measures

The exploratory outcome measures will include, but will not be limited to, the following:

- Confirmation and quantitation of CD22, CD79b and CD20 expression levels in either archival or freshly obtained (when available) tumor specimens (tumor biopsies, bone marrow biopsies, peripheral blood) by immunohistochemistry/flow cytometry/qRT-PCR
- Additional assessments related to the understanding of the mechanism of action of DCDT2980S, DCDS4501A and rituximab, mechanisms of resistance to DCDT2980S, DCDS4501A and rituximab, and/or NHL pathogenesis may be included
- Quality of life assessments using the M.D. Anderson Symptom Inventory (MDASI)

3.4 SAFETY PLAN

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

Safety will be evaluated through the monitoring of the following:

- Serious adverse events that are attributed to protocol-mandated interventions from the time of signing informed consent until the first dose of study treatment on Cycle 1, Day 1
- All adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A or rituximab whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from Cycle 1, Day 1 until 30 days after the last dose of DCDT2980S, DCDS4501A or rituximab whichever is later, including doses that were administered as part of crossover treatment
- All serious adverse events from the last dose of DCDT2980S, DCDS4501A or rituximab whichever is later, including doses that were administered as part of crossover treatment, and which is judged to be caused by DCDT2980S, DCDS4501A or rituximab, regardless of time of onset
- Measurements of protocol-specified hematology and clinical chemistry laboratory values
- Measurements of protocol-specified vital signs
- Assessment of ECGs
- Assessment of physical findings on clinical physical examinations

Patients who have an ongoing study drug-related adverse event will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, when it has been determined that the study treatment or participation is not the cause of the adverse event, or the study is terminated.

See Section 5.2.3 for assessment of causality for adverse events.

3.4.1 Internal Monitoring Committee (IMC)

This study will employ an Internal Monitoring Committee (IMC). The purpose of the IMC will be to make recommendations regarding study conduct on the basis of trial safety data to ensure patient safety while receiving study treatment.

The IMC will include a sponsor Medical Monitor not affiliated with the study, Drug Safety Scientist, biostatistician, and statistical programmer. Representatives from other Sponsor functional areas may be included as additional ad hoc members.

In addition to the ongoing assessment of the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities by the Investigator and the Medical Monitor, the IMC will review the aforementioned data at least twice during the study. The first planned review will occur after approximately 10 patients are randomized and have at least 6 weeks follow-up and the next formal review will occur when approximately 60 patients are randomized and have at least 6 weeks follow-up. Additionally, the IMC will meet as needed at the request of the Medical Monitor (e.g., based on unexpected safety signals). The IMC may make recommendations regarding study conduct, including but not limited to: performing additional safety analyses, amending the study protocol, holding patient enrollment to one or both treatment arms pending further safety evaluations, holding/discontinuing study treatment, or terminating the study.

Complete details of the IMC will be described in the IMC charter.

3.4.2 Risks Associated with DCDT2980S and DCDS4501A

The clinical safety profile of DCDT2980S and DCDS4501A based on clinical data obtained in the ongoing Phase I studies are summarized in Sections 1.2.1.2 and 1.2.2.2. Based on clinical data to date, the following known and suspected risks are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Sections 4.3.1 and 4.3.2.

Refer also to the Investigator Brochure for complete and updated details.

3.4.2.1 Infusion-Related Events

Some monoclonal antibodies may be associated with the development of allergic or anaphylactic reactions, to either the active protein or excipients. True allergic/anaphylactic reactions are rare after the first dose of a product, as they require prior sensitization. Patients with true allergic/anaphylactic reactions should not receive further doses of the product.

Monoclonal antibodies may also be associated with reactions that are clinically indistinguishable from true allergic/anaphylactic reactions, but which are mediated through direct release of cytokines or other pro-inflammatory mediators. Such reactions are often termed infusion-related reactions. Infusion-related reactions typically occur

with the first infusion of a monoclonal antibody product and are generally less frequent and/or less severe with subsequent infusions. They can often be managed by slowing the infusion rate and/or pre-treatment with various medications.

Allergic/anaphylactic reactions and infusion-related reactions typically begin during or within several hours of completing the infusion. The onset of symptoms may be rapid, and some reactions may be life threatening.

Patients should be monitored for these types of reactions during and after receiving DCDT2908S and DCDS4501A. DCDT2980S and DCDS4501A should be administered in an environment under close supervision of a physician and where full resuscitation facilities are immediately available. Specific guidelines for additional precautions to be taken during and following DCDT2980S and DCDS4501A administration are provided in Sections 4.3.1.5.

3.4.2.2 Tumor Lysis Syndrome

There is a potential risk of tumor lysis syndrome (TLS) if treatment with DCDT2980S or DCDS4501A results in the rapid destruction of a large number of tumor cells. If any evidence of this occurs during the study, tumor lysis prophylaxis measures will be instituted. Patients who are considered to have a high tumor burden (e.g., lymphocyte count $\geq 25 \times 10^9$/L) or bulky lymphadenopathy and who are considered to be at risk for tumor lysis by the investigator will receive tumor lysis prophylaxis (e.g., allopurinol ≥ 300 mg/day orally or a suitable alternative treatment according to institutional practice starting 12–24 hours prior to study treatment) and must be well hydrated prior to the initiation of study treatment at Cycle 1, Day 1. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion as deemed appropriate by the investigator.

3.4.2.3 Bone Marrow Toxicity/*Neutropenia*

Based on preclinical toxicity studies in rats and cynomolgus monkeys and clinical data from the ongoing Phase I studies DCT4862g and DCS4968g, neutropenia has been identified as a known risk (adverse drug reaction) of both DCDT2908S and DCDS4501A. Neutropenia and neutropenia-associated events were reversible but in some cases resulted in protocol-mandated dose reductions and/or delays.

Adequate hematologic function should be confirmed before initiation of study treatment. Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Treatment for hematologic toxicities may be delayed or modified as described in Section 4.3.1.

The use of G-CSF for neutropenia is described in Section 4.3.1.6. Transfusion support for anemia and thrombocytopenia is also permitted at the discretion of the treating physician.

3.4.2.4 Immunogenicity

As expected with any recombinant antibody, DCDT2980S and DCDS4501A may elicit an immune response and patients may develop antibodies against DCDT2980S and DCDS4501A. Patients will be closely monitored for any potential immune response to DCDT2980S and DCDS4501A. Appropriate screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with DCDT2980S or DCDS4501A. Considering the historically low immunogenicity rate of rituximab in NHL patients, ATAs against rituximab will not be monitored in this study.

3.4.2.5 Peripheral Sensory Neuropathy

Based on clinical data from the ongoing Phase I studies DCT4862g and DCS4968g and data from brentuximab vedotin, an anti-CD30-vc-MMAE ADC (see Section 3.4.2) peripheral sensory neuropathy has been identified as a known risk (adverse drug reaction) for both DCDT2980S and DCDS4501A.

Patients should be monitored for signs of neuropathy or worsening neuropathy and appropriate action taken per protocol guidelines. Study treatment dose and schedule modifications for significant and prolonged neuropathic toxicity and dose-reduction are described in Section 4.3.1.7.

3.4.2.6 Reproductive Toxicity

Adverse effects on human reproduction and fertility are anticipated with the administration of DCDT2980S and DCDS4501A given the mechanism of action of MMAE. Standard exclusion criteria will be used to ensure that patients of childbearing potential (male or female) are using adequate contraceptive methods.

3.4.2.7 *Hyperglycemia*

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other antibody-drug conjugates using the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of anti-hyperglycemic medications.

3.4.2.8 *Hepatotoxicity*

Hepatotoxicity is a potential risk of the ADCs. Definitive attribution of hepatotoxicity to the ADCs has not been established. Transient dose-related increases in hepatic enzyme levels were observed in rats treated with DCDT2980S and DCDS4501A. Elevations in transaminase and/or bilirubin levels requiring dose modifications have been reported in the ongoing clinical studies.

3.4.3 Risks Associated with Adcetris (Brentuximab vedotin)

An ADC using the same MMAE drug and linker as that used in DCDT2980S and DCDS4501A, but coupled to an antibody targeting the CD30 antigen (brentuximab vedotin, ADCETRIS™, Seattle Genetics), was recently approved by the FDA for use in

the treatment of specific subsets of patients with relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma.

The most common adverse reactions observed in studies with brentuximab vedotin (occurring in at least 20% of patients) were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting.

Serious adverse reactions were reported in 31% of patients receiving Adcetris. The most common occurring in > 2% of patients included peripheral motor neuropathy, abdominal pain, septic shock, supraventricular arrhythmia, pain in extremity and urinary tract information. In addition, JC virus infection resulting progressive multifocal leukoencephalopathy (PML) and death has been reported.

Due to the use of the same MMAE drug, it is possible that the adverse events observed with the use of brentuximab vedotin can also be observed with the use of DCDT2980S and DCDS4501A.

Refer to the current version of the ADCETRIS Prescribing Information for full and updated details.

3.4.4 Risks Associated with Rituximab Therapy and Their Management

3.4.4.1 Infusion Reactions

In single-agent clinical trials of rituximab and in postmarketing surveillance studies, mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first rituximab infusion. Other frequent infusion reaction signs and symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30–120 minutes of beginning the first infusion, and they resolved with slowing or interruption of the rituximab infusion and with supportive care (diphenhydramine, acetaminophen/ paracetamol, IV saline, meperidine, and vasopressors). The incidence of infusion reactions was highest during the first infusion and decreased with each subsequent infusion.

Rituximab has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with a time to onset of 30–120 minutes. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm and may require interruption of rituximab administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events (see Appendix D). Approximately 80% of fatal infusion reactions occurred in association

with the first infusion of rituximab. Because of this, patients should receive premedication with acetaminophen/paracetamol, antihistamines, or corticosteroids, in accordance with standard clinical practice, prior to rituximab infusions.

3.4.4.2 Management of Severe Infusion Reactions

Administration of rituximab will occur in a setting with emergency equipment and staff who are trained to monitor for and respond to medical emergencies. The rituximab infusion should be interrupted for severe reactions based on clinical judgment.

Medications and supportive care measures—including, but not limited to, epinephrine, antihistamines, glucocorticoids, IV fluids, vasopressors, oxygen, bronchodilators and acetaminophen/paracetamol—should be available for immediate use and instituted as medically indicated for use in the event of a reaction during administration.

In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during all rituximab infusions include those with preexisting cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events, and those with high numbers of circulating malignant cells ($\geq$25,000/μL) with or without evidence of high tumor burden.

3.4.4.3 Tumor Lysis Syndrome

Rapid reductions in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia have been reported within 12–24 hours after the first infusion of rituximab. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with rituximab. The risks of TLS appear to be greater in patients with high tumor burden. Patients deemed to be at high risk for TLS complications may at the investigator's discretion receive their initial dose of rituximab over 2 consecutive days (see Section 4.3.2.3). Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of TLS complications, rituximab has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

3.4.4.4 Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported for some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately 1 month after the last dose of rituximab. Patients with serologic findings consistent with chronic HBV (Hepatitis B surface antigen [HBsAg] positivity) or hepatitis C virus (HCV) infection (HCV RNA or

antibody positivity) are ineligible for this study. Patients who are not chronically infected with HBV but have serologic evidence of prior infection at baseline (IgG anti-HBc positive, but HBV DNA negative) may be eligible (if believed to be in the patient's best interest by the investigator and Medical Monitor) and would be monitored closely for perturbations in liver function during the period of rituximab treatment and every 2–4 weeks thereafter. Such patients would also be required to receive prophylactic anti-viral therapy with lamivudine for at least 6 months after completion of rituximab therapy (Yeo et al. 2009).

Additional serious viral infections, new, reactivated, or exacerbated (e.g., infections caused by cytomegalovirus, varicella zoster virus, herpes simplex virus, West Nile virus, parvovirus B19, JC virus, and HCV) have been reported with rituximab, mainly in patients who had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Particular attention should be given to patients who have had significant prior immunosuppressive treatment such as high-dose chemotherapy and stem cell transplant. JC virus infection resulting in progressive multifocal leukencephalopathy (PML) and death has been observed in rituximab-treated patients with hematologic malignancies or with autoimmune diseases. Most cases of PML were diagnosed within 12 months of the patient's last infusion of rituximab. Physicians should consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. Physicians should discontinue rituximab (and DCDT2980S and/or DCDS4501A) and consider discontinuation or reduction of any immunosuppressive therapy in patients who develop PML.

3.4.4.5 Cardiovascular Events

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with preexisting cardiac conditions, including arrhythmias and angina have had recurrences of these events during rituximab therapy should be monitored throughout the infusion and the immediate post-infusion period.

3.4.4.6 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, were observed in patients receiving rituximab in combination with chemotherapy for DLBCL. In post-marketing reports, which include patients with low-grade or follicular NHL and patients with DLBCL, the mean time to onset of symptoms was 6 days (range, 1–77 days) in patients with documented gastrointestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

3.4.4.7 Immunization

The safety of immunization with live viral vaccines following rituximab therapy has not been studied. Patients who participate in this study may not receive either primary or booster vaccination with live virus vaccines for at least 6 months prior to initiation of rituximab or at any time during study treatment. Investigators should review the vaccination status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult vaccination with non-live vaccines intended to prevent infectious diseases prior to study therapy.

Refer to the Rituxan®/MabThera® (Rituximab) Package Insert/SmPC for additional safety information.

3.5 MINIMIZATION OF BIAS

This is a randomized, non-comparative, open-label study. Patients will be randomly allocated to two treatment arms in a 1:1 ratio through use of an Interactive Voice and Web Response System (IXRS). A dynamic stratified randomization scheme will be employed to ensure balance in the stratification factors as specified in Section 3.1.

3.6 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche group, will Sponsor this study. A Contract Research Organization (CRO) will be utilized to perform project management, study management and clinical monitoring. Genentech will conduct CRO oversight, approve patient eligibility, perform dose escalation decision-making, medical monitoring, and statistical programming and analysis. An Internal Monitoring Committee (IMC; see Section 3.4) will provide an additional level of safety monitoring for the study.

Approximately 40 study centers in the United States, Canada, and Europe will participate in the study to enroll approximately 120 patients. Additional patients may be enrolled in order to obtain additional safety and/or efficacy data.

Electronic data capture (EDC) will be utilized for this study. An IXRS will be used to assign patient numbers. A central laboratory will be used for sample management and storage until shipment to one of several specialty laboratories or GNE for analysis. An independent review facility (IRF) will be used for the collection and possible assessment of radiographic images from tumor assessments. Additional vendors for ECG collection and possible analysis and for PRO collection and data entry will be used.

3.7 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with the U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws, as well as other applicable country laws.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria to be eligible for study entry:

- Signed Informed Consent Form(s)
- Age $\geq$ 18 years
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Life expectancy of at least 12 weeks
- History of histologically documented relapsed or refractory Grades 1–3a FL, or relapsed or refractory DLBCL
- Availability of an archival or freshly biopsied tumor tissue sample must be confirmed for study enrollment.
- Have a clinical indication for treatment as determined by the investigator
- Must have at least one bi-dimensionally measurable lesion ($>$ 1.5 cm in its largest dimension by CT scan or MRI)
- Laboratory values (including patients with hepatic or renal involvement), as follows:

  AST and ALT $\leq 2.5 \times$ the upper limit of normal (ULN)

  Total bilirubin $\leq 1.5 \times$ ULN

  Platelet count $\geq$ 75,000/mm^3 (unless thrombocytopenia clearly due to marrow involvement of NHL, and/or disease-related immune thrombocytopenia)

  Absolute neutrophil count $\geq$ 1000/mm^3 (without growth factor support, unless neutropenia clearly due to marrow involvement of NHL)

  Total hemoglobin $\geq$ 9 g/dL (without transfusion support >14 days prior to screening, unless anemia clearly due to marrow involvement of NHL)

  Serum creatinine $\leq$ 2.0 mg/dL or measured creatinine clearance $\geq$ 50 mL/min

- *For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement to use one highly effective form of nonhormonal contraceptionor two effective forms of nonhormonal contraception,* ***including at least one method with a failure rate of <1% per year*** *through the course of study treatment and for at least 3 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later) in women and at least 5 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later) in men.*

  A woman is considered not to be of childbearing potential if she is postmenopausal, defined by amenorrhea of $\geq$12 months duration and age $\geq$45 years, or has undergone hysterectomy and/or bilateral oophorectomy.

The following are considered highly effective forms of contraception: 1) true abstinence; 2) male sterilization (with postprocedure documentation of absence of sperm in the ejaculate). For female patients, the sterilized male partner should be the sole partner.

The following are considered effective forms of contraception: 1) intrauterine device (copper IUD or hormonal IUDs only) or intrauterine system; 2) condom with spermicidal foam/gel/film/cream/suppository; 3) occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.

Males must agree to abstain from sperm donation for at least 5 months after the last dose of DCDT2980S or DCDS4501A or rituximab (whichever is later).

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Prior use of any monoclonal antibody, radioimmunoconjugate or antibody-drug conjugate within 4 weeks before Cycle 1, Day 1
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational anti-cancer agent within 2 weeks prior to Cycle 1, Day 1

  Adverse events except for sensory neuropathy from any previous treatments must be resolved or stabilized to Grade ≤ 2 prior to Cycle 1, Day 1
- Completion of autologous stem cell transplant within 100 days prior to Cycle 1, Day 1
- Prior allogeneic stem cell transplant
- Eligibility for autologous SCT (patients with relapsed or refractory DLBCL)
- History of transformation of indolent disease to DLBCL
- History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma, e.g., of the cervix or breast, are allowed. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥2 years prior to Cycle 1, Day 1.
- Current or past history of CNS lymphoma
- Current Grade > 1 peripheral neuropathy

- Evidence of significant, uncontrolled concomitant diseases which could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Recent major surgery within 6 weeks prior to Cycle 1, Day 1, other than for diagnosis
- Presence of positive test results for Hepatitis B (HBsAg and/or total Hepatitis B core antibody [anti-HBc]) or Hepatitis C (HCV antibody)

  Patients who are positive for anti-HBc are eligible only if PCR is negative for HBV DNA and it is believed by both the investigator and Medical Monitor to be in the patient's best interest to participate.

  Patients who are positive for HCV antibody must be negative by for HCV by PCR to be eligible for study participation
- Known history of HIV seropositive status
- Women who are pregnant or lactating
- Ongoing corticosteroid use >30 mg/day prednisone or equivalent

  Patients receiving corticosteroid treatment ≤ 30 mg/day prednisone or equivalent must be documented to be on a stable dose prior to study enrollment and initiation of therapy

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor via facsimile and obtain the Sponsor's approval to enroll the patient. Once the Sponsor reviews and approves the patient for enrollment, the patient number will be assigned via IXRS.

As described in Section 3.1.2, only select investigator sites that have agreed to participate in the nonrandomized portion of the study will enroll patients into these cohorts. Cohorts C and D will be opened sequentially following completion of the randomized portion of the study for follicular lymphoma patients.

Personnel responsible for performing PK and ATA assays will be receive participants' treatment assignments to identify appropriate PK and ATA samples to be analyzed in the appropriate corresponding assays.

4.3 STUDY TREATMENT

4.3.1 DCDT2980S and DCDS4501A

4.3.1.1 Formulation and Storage

a. DCDT2980S

DCDT2980S will be provided as a lyophilized powder in a single-use 20-cc vial. The solution for reconstitution is Sterile Water for Injection (SWFI) and the reconstitution volume is 2.6 mL to yield a final concentration of 20 mg/mL DCDT2980S in 40 mM L-histidine hydrochloride, 240 mM sucrose, and 0.02% polysorbate 20, pH 6.0.

Reconstituted DCDT2980S should be further diluted with sterile 0.9% NaCl to a total volume of 250 mL.

DCDT2980S vials must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. DCDT2980S should not be used beyond the expiration date provided by the manufacturer. Vial contents should not be frozen or shaken and should be protected from direct sunlight. After reconstitution, DCDT2980S vials may be stored at room temperatures (> 8°C–25°C [> 46°F–77°F]) for up to 4 hours, or at refrigerated temperatures (2°C–8°C [36°F–46°F]) for up to 8 hours prior to use. Once DCDT2980S has been diluted with sterile 0.9% NaCl, the solution should be used within 4 hours at room temperature or within 8 hours at refrigerated temperature. Vials are intended for single use only; therefore, any remaining solution should be discarded.

For further details, refer to the DCDT2980S Investigator Brochure.

b. DCDS4501A

DCDS4501A is provided as a liquid formulation and contains no preservatives. Each single-use, 20-cc vial is filled to deliver 100 mg of DCDS4501A. The Drug Product is formulated as 10 mg/mL DCDS4501A in 20 mM L-histidine acetate, 240 mM sucrose, 0.02% (w/v) polysorbate 20, pH 5.5.

DCDS4501A will be administered to patients by IV via syringe pump with IV infusion set containing a 0.22 µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight.

DCDS4501A vials must be refrigerated at 2–8°C (36–46°F) upon receipt until use. *DCDS4501A vials may be stored at room temperature (> 8°C to 25°C [46°F–77°F]) for up to 8 hours.* DCDS4501A should not be used beyond the expiration date provided by the manufacturer. Vial contents should not be frozen or shaken and should be protected from direct sunlight. *Vials are intended for single use only; therefore, any remaining solution should be discarded.*

Once the DCDS4501A dose solution has been prepared, the solution should be used within 4 hours at room temperature (> 8°C to 25°C [46°F–77°F]) *or within 8 hours refrigerated at 2°C–8°C (36°F–46°F).* Because the Drug Product contains no

preservatives, the Sponsor recommends using DCDS4501A in a syringe and extension set as soon as possible to reduce the risk of microbial contamination.

For further details, refer to the DCDS4501A Investigator Brochure.

4.3.1.2 Dosage and Administration

a. DCDT2980S-Specific Information

DCDT2980S will be administered to patients by IV infusion. Compatibility testing has shown that DCDT2980S is stable when diluted in polyvinyl chloride (PVC) bags to a concentration at or above 0.04 mg/mL in 0.9% NaCl diluent. The Drug Product will be delivered following dilution in 0.9% NaCl with a final DCDT2980S concentration determined based on dose and patient weight. The study drug will be diluted in a PVC bag and delivered using a 0.22 µm in-line filter on the IV infusion set.

Additional information/instructions regarding study drug administration will be provided in the Pharmacy Binder.

b. DCDS4501A-Specific Information

DCDS4501A will be administered to patients by IV via syringe pump with IV infusion set containing a 0.22 µm in-line filter with a final volume of DCDS4501A determined by the dose and patient weight. Compatibility testing has shown that DCDS4501A is stable in both syringes made of polypropylene (PP) and in standard extension sets with 0.22 µm in-line filter, when stored neat or diluted with 0.9% NaCl saline.

Additional information/instructions regarding study drug administration will be provided in the Pharmacy Binder.

c. General Information

The total dose of DCDT2980S and DCDS4501A for each patient will depend on the patient's weight within 96 hours prior to Day 1 of each cycle. The patient weight obtained during screening may be used for dose determination at all treatment cycles; if the patient's weight within 96 hours prior to Day 1 of a given treatment cycle differs by >10% from the weight obtained during screening, then the new weight should be used to calculate the dose.

For both DCDT2980S and DCDS4501A, the initial dose will be administered to well-hydrated (based on clinical judgment) patients over 90 (± 10) minutes. Pre-medication with acetaminophen or paracetamol (e.g., 500–1000 mg) and diphenhydramine (e.g., 50–100 mg) per institutional standard practice may be administered prior to each infusion. Administration of corticosteroids is permitted at the discretion of the treating physician. For patients who do not receive pre-medications prior to the first dose of DCDT2980S and who develop an infusion related reaction during the first dose should receive pre-medications prior to subsequent doses (see Table 1).

The DCDT2980S/DCDS4501A infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. Following the initial dose, patients will be observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If the infusion is well-tolerated, subsequent doses of DCDT2980S/DCDS4501A may be administered over 30 (± 10) minutes, followed by a 30-minute observation period post-infusion.

For instructions on study drug preparation and administration, refer to the DCDT2980S and DCDS4501A Investigator Brochure.

4.3.1.3 Dosage Modification

Patients should be assessed clinically for toxicity prior to each dose using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 grading scale. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable. If scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date, with subsequent dosing continuing on a 21-day schedule as applicable.

Specific guidelines around dosage modifications for neutropenia and peripheral neuropathy are detailed below in Sections 4.3.1.6 and 4.3.1.7. Patients who experience other treatment-related Grade 3 or 4 toxicity or laboratory abnormalities will be allowed to delay dosing of study treatment (both ADC and rituximab) for up to 2 weeks to allow for recovery. Patients may continue to receive additional infusions of DCDT2980S or DCDS4501A per their treatment assignment provided that the toxicity has resolved to Grade ≤ 2 or $\geq 80\%$ of the baseline value, whichever is lower within the 2 week delay period. Upon resolution, the dose for subsequent infusions may be reduced to 1.8 mg/kg. If the toxicity that resulted in the dose reduction persists or recurs at the reduced dose, then the patient should be discontinued from study treatment. The decision for dose modification will be made based on the investigator's assessment of ongoing clinical benefit with continuing study treatment and in consultation with the Medical Monitor.

Once dose reductions of DCDT2980S or DCDS4501A are made *for toxicity*, dose re-escalation will not be allowed. *Patients who are enrolled in the nonrandomized portion of the study (Cohorts C and D), are dosed at an ADC dose of 1.8 mg/kg, and have progressive disease in the absence of any drug-related toxicity may have their ADC dose increased to 2.4 mg/kg if it is felt that there is reasonable justification for ongoing clinical benefit. The decision to increase the dose must be made in consultation with and approval of the Medical Monitor.*

If a patient develops unacceptable toxicity to DCDT2980S or DCDS4501A requiring its discontinuation, single-agent rituximab may be continued based on the investigator's assessment of ongoing clinical benefit and with the approval of the Medical Monitor.

4.3.1.4 Schedule Modification

Patients in whom toxicities have not resolved to Grade ≤ 2 or $\geq 80\%$ of baseline value, whichever is lower, may have their study treatment delayed by up to 2 weeks. Dosing of both DCDT2980S or DCDS4501A and rituximab should be held during this period. If all study drug–related toxicities have resolved sufficiently, the patient may resume DCDT2980S or DCDS4501A and rituximab dosing on the regular every-21-day schedule.

A patient's dosing may be changed to a 28-day cycle if it is felt by the investigator that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from a transient and reversible toxicity e.g., cytopenia without requiring repeated treatment delays. Modifications to the dosing schedule in this fashion must be made in consultation with and with the approval of the Medical Monitor.

Patients who do not fulfill the criteria for continuation of dosing after the 2-week delay may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.5). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

Specific guidelines around schedule modifications for neutropenia and peripheral neuropathy are detailed below in Sections 4.3.1.6 and 4.3.1.7.

4.3.1.5 Infusion Reaction

Patients will be monitored during and after each DCDT2980S/DCDS4501A infusion for 90 minutes after the first infusion and for 30 minutes after subsequent infusions in the absence of infusion-related adverse events. Patients who experience infusion-related symptoms should be managed as described in Table 1. Precautions for suspected anaphylactic reaction during study drug infusions are provided in Appendix D.

In the event of a life-threatening infusion-related reaction (IRR), which may include pulmonary or cardiac events, or an IgE-mediated anaphylactic reaction, administration of DCDT2980S/DCDS4501A should be immediately discontinued. Patients who experience these reactions should receive aggressive symptomatic treatment and are not eligible to receive any additional study treatment.

Premedication prior to DCDT2980S/DCDS4501A with acetaminophen/paracetamol, antihistamines, or corticosteroids per standard clinical practice is permitted, e.g., in patients with substantial tumor burden and where the risk of cytokine release syndrome is high. In patients who do not receive premedication prior to any given dose of DCDT2980S/DCDS4501A and who develop any Grade ≥ 2 infusion-related toxicity, premedication should be administered prior to subsequent doses.

4.3.1.6 Neutropenia

Because neutropenia is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.2.3), the use of growth factor support (G-CSF) as prophylactic and therapeutic indications is permitted (see Appendix F) in order to allow continued dosing of DCDT2980S/DCDS4501A. Dose modifications for patients who experience treatment-related Grade 3–4 neutropenia in the context of G-CSF usage are as follows:

- Primary prophylaxis with G-CSF, i.e., prior to the first dose of DCDT2980S/DCDS4501A, is permitted for patients with clinical factors listed in Appendix F or who otherwise are considered at high risk for developing neutropenia on study treatment.
- Patients who experience treatment-related Grade 3–4 neutropenia will be allowed to delay dosing of study treatment (both ADC and rituximab) for up to two weeks to allow for recovery. Therapeutic G-CSF is permitted as clinically indicated (see Appendix F) and to facilitate neutrophil recovery to allow subsequent DCDT2980S/DCDS4501A dosing.
- Subsequent dosing DCDT2980S/DCDS4501A is permitted provided that the neutropenia has resolved to Grade ≤ 2, or $\geq 80\%$ of the baseline value, whichever is lower, within the 2-week period.
- If prophylactic G-CSF was not administered prior to the cycle in which the Grade 3–4 neutropenia developed, then prophylactic G-CSF may be administered prior to subsequent cycles without DCDT2980S/DCDS4501A dose reduction. The dose schedule may be changed from 21-day to 28-day cycles to provide sufficient time for neutrophil recovery in subsequent cycles. In the absence of prophylactic G-CSF or dose schedule modification, the dose of DCDT2980S/DCDS4501A in subsequent cycles should be reduced to 1.8 mg/kg.
- If Grade 3–4 neutropenia recurs with prophylactic G-CSF, the dose for subsequent DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg. Prophylactic G-CSF and dose schedule modifications as described above are permitted in order to maintain the reduced DCDT2980S/DCDS4501A dose level and schedule.
- If Grade 3–4 neutropenia recurs at the reduced dose despite the administration of prophylactic G-CSF, then the patient should be discontinued from study treatment.
- *For patients enrolled into the nonrandomized portion of the study (Cohorts C and D), dose modifications will not be allowed. Administration of therapeutic/prophylactic G-CSF and dose-schedule modifications as described above are allowed. Patients who have persistent or recurrent Grade 3–4 neutropenia as defined above should be discontinued from study treatment.*

The determination of the dose and schedule modifications will be made based on the investigator's assessment of ongoing clinical benefit with continuing study treatment and with the approval of the Medical Monitor.

4.3.1.7 Peripheral Sensory Neuropathy

Peripheral sensory neuropathy is a known risk of DCDT2980S and DCDS4501A (see Section 3.4.2.5). For new or worsening drug-related Grade 2 or 3 peripheral sensory neuropathy, dosing should be held for up to 2 weeks until peripheral sensory neuropathy improves to Grade 1 or baseline grade. Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and approval of the Medical Monitor based on an assessment of the risk-benefit analysis of continuing to delay study treatment.

Following resolution of peripheral sensory neuropathy, subsequent doses of DCDT2980S/DCDS4501A should be reduced to 1.8 mg/kg. If worsening Grade 2 or 3 peripheral sensory neuropathy recurs following dose reduction, study treatment should be discontinued. For Grade 4 peripheral sensory neuropathy, study treatment should be discontinued.

For patients enrolled into the nonrandomized portion of the study (Cohorts C and D), dose modifications will not be allowed. Patients who have Grade 2 or 3 peripheral sensory neuropathy as defined above should be discontinued from study treatment.

4.3.1.8 *Hyperglycemia*

Hyperglycemia has been observed in patients treated with DCDT2980S and DCDS4501A as well as with other antibody-drug conjugates using the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation of improved anti-hyperglycemic medications (see Section 3.4.2.7).

For symptomatic fasting Grade 3 (>250–500 mg/dL) or asymptomatic Grade 4 (>500 mg/dL) hyperglycemia, medical management should be initiated immediately and consultation with a specialist should be considered. If the hyperglycemia persists for >1 week after initiation of management, dose modification, schedule modification, or discontinuation of study treatment should be considered. In these cases the study Medical Monitor should be consulted to assess the risk-benefit balance of continued study treatment.

Table 1 Management of Infusion-Related Symptoms

Infusion-Related Symptoms [a]	Guidance
Grade 1–2	• Slow or hold infusion • Give supportive treatment [b] • Upon symptom resolution, may resume/escalate infusion rate at the investigator's discretion [c]. Note: For Grade 2 wheezing or bronchospasm, patient must be pre-medicated for subsequent doses. If symptoms recur with the same or greater severity, the infusion must be stopped immediately and study treatment permanently discontinued.
Grade 3	• Discontinue infusion • Give supportive treatment [b] • Upon symptom resolution, may resume/escalate infusion rate at the investigator discretion [c] Note: Patients must be pre-medicated prior to subsequent study treatment. If symptoms recur with the same or greater severity, the infusion must be stopped immediately and study treatment permanently discontinued. If patient has Grade 3 wheezing or bronchospasm at first occurrence, study treatment should be permanently discontinued.
Grade 4	• Discontinue infusion immediately, treat symptoms aggressively, and permanently discontinue patient from study treatment

IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Refer to the NCI CTCAE, v4.0 scale for the grading of symptoms. Management of IgE-mediated allergic reactions should be as directed in the text following this table.

[b] Supportive treatment: Patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the last 4 hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators. Patients with hypotension requiring vasopressor support must be permanently discontinued from study drug.

[c] Infusion rate escalation after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hr every 30 minutes.

4.3.2 Rituximab

4.3.2.1 Formulation

Rituximab (Rituxan®/MabThera®) is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in 500-mg (50-mL) single-use vials. A single-unit, 500-mg carton contains one 50-mL vial of rituximab (10 mg/mL). The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, and 0.7 mg/mL polysorbate 80, after reconstitution with SWFI. The pH is adjusted to 6.5. Vials are for single use. Each vial and carton will contain a label (either single-panel or booklet) affixed to the vial or carton.

4.3.2.2 Dosage, Administration, and Storage

Rituximab (Rituxan®, MabThera®) will be administered intravenously once per 3-week (or 4-week) cycle. The infusion at 375 mg/m^2 for each dose will be based on the patient's body surface area at screening and will remain the same throughout the study.

If a scheduled dose of rituximab falls outside of the ±2-day window for reasons other than an adverse event, the site must notify and discuss with the Genentech Medical Monitor prior to rituximab administration. Such dosing may not necessarily qualify as a protocol deviation, if deemed to be in the best interests of the patient, after consultation with the Medical Monitor and agreed to in advance by the Medical Monitor.

Rituximab should not be administered as an IV push or bolus. Infusion reactions may occur. Premedication consisting of acetaminophen (or paracetamol), diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (e.g., up to 100 mg or an equivalent dose of methylprednisolone) may also be administered beginning with the first infusion, per standard clinical practice. Premedication may attenuate infusion reactions. Because transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

a. First Infusion

The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If infusion reactions do not occur, the infusion rate should be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

b. Subsequent Infusions

If the patient tolerates the first infusion well, subsequent rituximab infusions may be administered at an initial rate of 100 mg/hr and increased in 100 mg/hr increments at 30-minute intervals to a maximum of 400 mg/hr, as tolerated. If the patient does not tolerate the first infusion well, the guidelines for the first infusion should be followed.

If a patient tolerates the first three cycles of study treatment without significant infusion reactions, rituximab may be administered as "rapid infusion" in accordance with local institutional guidelines.

c. Storage

Rituximab vials must be stored at 2°C–8°C (36°C–46°F). Rituximab vials should be stored in the outer carton in order to protect them from light. Rituximab solution for infusion may be stored at 2°C–8°C (36°C–46°F) for 24 hours and has been shown to be stable for an additional 12 hours at room temperature. However, since rituximab does not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C).

No incompatibilities between rituximab and PVC or polyethylene bags have been observed.

See the Rituxan® (Rituximab) Package Insert or SmPC (in the E.U.) for additional information.

4.3.2.3 Dosage Modification

There will be no rituximab dose modification in this study. Patients at high risk for TLS complications (see Section 3.4.2.2) may, at the investigator's discretion, receive their initial dose of rituximab over 2 consecutive days (e.g., 125 mg/m^2 on Day 1, 250 mg/m^2 on Day 2; with DCDT2980S/DCDS4501A dose potentially delayed to Day 3).

Any NCI CTCAE, v4.0, toxicity Grade ≥ 3 in severity that is deemed related to rituximab treatment will require interruption of study treatment (both ADC and rituximab) until resolution to Grade ≤ 2 or $\geq 80\%$ of baseline, whichever is lower. Resumption of rituximab treatment may be considered in patients with resolution of toxicities to Grade ≤ 1 within 2 weeks at the discretion of the investigator, after consultation with the Medical Monitor. Failure of such toxicities to resolve after 2-week delay in study treatment will require permanent discontinuation of rituximab. Continuation of rituximab treatment may be permitted on the basis of ongoing clinical benefit following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor.

If a patient develops unacceptable toxicity to rituximab requiring its discontinuation, single-agent DCDT2980S or DCDS4501A may be continued based on the investigator's assessment of ongoing clinical benefit and with the approval of the Medical Monitor.

4.3.2.4 Schedule Modification

Patients in whom toxicities have not resolved (i.e., to Grade ≤ 1 or $\geq 80\%$ of baseline) may have their study treatment delayed by up to 2 weeks. If after the up to 2-week delay all study drug–related toxicities have resolved sufficiently, the patient may receive the scheduled doses of rituximab. In addition, a patient's dosing may be changed to a 28-day cycle if it is felt by the investigator and Medical Monitor that changing a patient's dosing regimen from 21-day to 28-day cycles would provide sufficient time for recovery from transient cytopenias without requiring repeated treatment delays.

Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed may be discontinued from study treatment and be followed for safety outcomes (see Section 4.5.5). Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

4.3.2.5 Infusion Reaction

Patients will be monitored during and after each rituximab infusion for 90 minutes after the first infusion and for 30 minutes after subsequent infusions in the absence of infusion-related adverse events. Patients who experience infusion-related symptoms should be managed as directed in Table 1 (see Section 4.3.1.5).

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction to rituximab, rituximab should be discontinued and no additional rituximab should be administered. Patients who experience these reactions should receive aggressive symptomatic treatment and should be discontinued from study treatment.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the end of study visits. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF).

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Concomitant use of hematopoietic growth factors is allowed in accordance with instructions provided in the package inserts.

Patients who experience infusion-related temperature elevations of $> 38.5°C$ ($> 101.3°F$) or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol ($\geq$ 500 mg) and/or H1 and H2 histamine-receptor antagonists (e.g., diphenhydramine, ranitidine). Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with additional supportive therapies (e.g., supplemental oxygen, β2-agonists, and/or corticosteroids) as clinically indicated according to standard clinical practice (see Table 1).

Infusion reaction prophylaxis with medications (e.g., acetaminophen/paracetamol, antihistamines, and/or corticosteroids) may be instituted at any point in the study if it is determined to be in the best interest of the patient based on observation of IRRs in patients already enrolled in the study. Patients with Grade 3 hypotension or fever must be pre-medicated prior to retreatment (see Section 4.3.1.5). Patients with hypotension requiring vasopressor support, or with Grade 3 wheezing, hypoxia, or generalized urticaria, must be permanently discontinued from study treatment.

4.4.2 Excluded Therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy
- Immunotherapy including immunosuppressive therapy
- Radioimmunotherapy
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Biologic agents (other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts); guidelines for the use of G-CSF are detailed in Section 4.3.1.6 and Appendix F.
- Any therapies intended for the treatment of lymphoma or leukemia, whether approved by local regulatory authorities or investigational

Patients who require the use of any of these agents will be discontinued from all study treatment. Patients who are discontinued from study treatment will be followed for safety outcomes for 30 days following the patient's last dose of DCDT2980S or DCDS4501A or rituximab, whichever is later, or until the patient receives another anti-cancer therapy whichever occurs first.

4.5 STUDY ASSESSMENTS

4.5.1 Definitions of Study Assessments

4.5.1.1 Medical History and Demographics

Medical history includes all clinically significant diseases, prior cancer history, prior cancer therapies and procedures, and all medications used by the patient within 7 days preceding the screening visit.

4.5.1.2 Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure while the patient is in a sitting or semi-supine position, pulse oximetry, pulse rate, and body temperature. Every effort will be made to ensure that vital signs are obtained from patients in a consistent manner and position. The timing of vital sign collection on the days of study treatment administration is as follows:

- For the administration of rituximab, vital signs should be assessed prior to the start of the infusion, every 15 ($\pm$5) minutes during the first hour of the infusion, as clinically indicated during the remainder of the infusion, and following the completion of the infusion.

- For the administration of DCDT2980S or DCDS4501A, vital signs should be assessed prior to the start of the infusion, every 15 (±5) minutes during the infusion, at the end of the infusion, and every 30 (±10) minutes for 90 minutes post-infusion following dosing at Cycle 1 and 30 (±10) minutes following dosing in subsequent cycles.

Additional monitoring of vital signs should be performed if clinically indicated.

4.5.1.3 Physical Examination

A complete physical examination should include the evaluation of head, eye, ear, nose, and throat; cardiovascular; dermatological; musculoskeletal; respiratory; gastrointestinal; and neurological systems.

Targeted physical examinations should be limited to systems of clinical relevance (i.e., cardiovascular, respiratory, and any system that might be associated with tumor assessment, such as lymph nodes, liver, and spleen) and those systems associated with symptoms.

Changes from baseline should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

4.5.1.4 Laboratory Assessments

On days of study drug administration, pre-infusion laboratory samples should be drawn within 4 hours prior to the start of infusion unless otherwise specified. Local laboratory assessments may be obtained up to 72 hours prior to the start of study treatment administration (see below and Section 4.5.3). Instruction manuals and supply kits will be provided for all central laboratory assessments.

Central Laboratory Assessments

Samples for flow cytometry, PK, bone marrow, and anti-DCDT2980S or anti-DCDS4501A antibody assessments will be sent to one or several laboratories or to Genentech for analyses (see Section 3.6):

- Leukocyte immunophenotyping/flow cytometry (fluorescence-activated cell sorting [FACS] lymphocyte subsets)

  Whole-blood samples will be collected to analyze B-cell subsets ($CD19^+$), T-cell counts ($CD3^+$, $CD4^+$, $CD8^+$), and NK cell counts ($CD16^+$, $CD56^+$), by flow cytometry.

- ATA assays

  ATAs to DCDT2980S or DCDS4501A will be determined at Genentech using a validated ELISAs (see Section 4.9).

- PK assays (see Section 4.5.1.6)
- A plasma sample will be collected from patients for exploratory research as indicated in Section 4.5.1.9.

- For patients who sign the optional consent, a blood sample will be collected prior to the first dose of study treatment for exploratory research.
- Tumor tissue sample (archival or fresh) will be collected from patients for central pathologic review as described in Sections 4.1.1 and 4.5.1.9.

Local Laboratory Assessments

Samples for hematology, serum chemistry, liver function, and pregnancy will be analyzed at the study site's local laboratory. Local laboratory assessments may be obtained up to 72 hours prior to start of study treatment administration on Day 1 of the treatment cycle.

- Hematology: Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells)
- Coagulation: aPTT, prothrombin time (PT), and INR
- Quantitative immunoglobulins (IgA, IgG, and IgM)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH) and uric acid

  Serum gamma-glutamyl transpeptidase (GGT) levels will be required at screening only
- Hemoglobin A1c
- Viral serology and detection (screening assessment only and if clinically indicated)

  Hepatitis B (HBsAg and HBcAb; also HBV DNA by PCR if the patient is HBcAb positive)

  HCV antibody
- Pregnancy test

  For women of childbearing potential (see Section 4.1.2), a serum pregnancy test must be performed within 14 days prior to Cycle 1, Day 1.

  Urine pregnancy tests will be performed during the study treatment period. If any urine test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Any patient with a positive serum test will not be allowed to receive any study treatment.

4.5.1.5 Electrocardiogram Assessments

Twelve-lead digital ECG measurements will be obtained in triplicate, with immediately consecutive ECGs obtained until three evaluable ECGs are recorded, at the following timepoints:

- Screening
- 30–60 minutes before the start of DCDT2980S or DCDS4501A infusion in Cycle 1
- 30–60 minutes after the completion of DCDT2980S or DCDS4501A infusion in Cycle 1
- 30–60 minutes after the completion of DCDT2980S or DCDS4501A infusion in Cycle 3
- Day 8 (±1 day) of Cycle 3 time-matched, i.e., obtained at the same time of day, with post-DCDT2980s/DCDS4501A infusion ECGs for Cycle 3
- Treatment completion/early termination visit

Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction.

All ECGs as described above will be submitted to a Sponsor-designated ECG central laboratory for storage and potential analysis. Detailed instructions on ECG acquisitions and transmissions to the ECG central laboratory will be provided in the ECG manual provided for this study.

Representative ECGs at each timepoint should be reviewed by the investigator or a qualified designee. Post-screening ECG measurements should be obtained as close as possible to scheduled serum and plasma PK samples (see Appendices B-1 and B-2) and should be no more than 30 minutes apart. If QTc prolongation ($>$500 msec *and* >60 msec longer than the pre-dose baseline value) is noted, ECGs should be repeated until the prolongation is reversed or stabilized. If a PK sample is not scheduled at the timepoint where QTc prolongation is first observed, then an unscheduled sample should be obtained. An evaluation for potential causes of QT prolongation e.g., electrolyte imbalances or concomitant medications, should be performed, study treatment dosing held, and the Medical Monitor notified. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician.

4.5.1.6 Pharmacokinetic Assessments

Pharmacokinetics of DCDT2980S and DCDS4501A will be characterized by measuring total antibody (conjugated and unconjugated antibody), antibody-conjugated MMAE (acMMAE), and free MMAE concentrations using validated methods (see Section 4.9). Plasma samples may also be analyzed for other potential MMAE containing catabolites, per sponsor's discretion. Pharmacokinetics of rituximab will be characterized by measuring rituximab concentrations using a validated method (see Section 4.9). These

assessments will allow for further characterization of PK of DCDT2980S and DCDS4501A, the assessment of the drug interaction potential when they are given in combination with rituximab, and the investigation of potential correlations between PK parameters and safety and/or activity if data allow and at the sponsor's discretion.

4.5.1.7 Immunogenicity Assessments

The immunogenicity evaluation will utilize a risk-based strategy and tiered approach (Rosenberg and Worobec 2004a; 2004b, 2005, Koren et al. 2008) designed to detect and characterize all anti-therapeutic antibody (ATA) responses to DCDT2980S and DCDS4501A. Patient samples will be first screened to detect all antibody responses toward DCDT2980S or DCDS4501A. Samples that screen positive will be analyzed in a confirmatory assay (competitive binding with DCDT2980S or DCDS4501A) to assess the specificity of the positive response. Titers will be determined for confirmed positive samples. Further characterization will be assessed by competitive binding with the monoclonal antibody (mAb) component of DCDT2980S or DCDS4501A to characterize if the ATA responses are primarily to the mAb or the linker-drug regions of the ADC. Positive ATA samples will be stored for further characterization of ATA responses, if necessary.

The schedule of sample collection for ATA assessment is outlined in Appendices B-1 and B-2, depending on the schedule of study treatment administration. Samples for ATA will not be collected during the crossover treatment period.

4.5.1.8 Tumor Response Assessments

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, based on physical examinations, CT and/or MRI scans, and bone marrow examinations, using standard response criteria for NHL (Cheson et al. 2007) (see Appendix C).

a. Radiographic Assessments

CT scans with contrast should include chest, abdomen, and pelvis scans; CT scans of the neck should be performed at screening and followed only if disease is present at screening. Post-screening radiographic assessments may be limited to areas of prior involvement only if required by local health authorities.

MRI scans may be used instead of CT scans in patients for whom CT scans with intravenous contrast are contraindicated. Details regarding imaging procedures in these cases will be provided in the Imaging Manual.

An ^{18}F-FDG-PET (hereafter referred as PET) scan is required during screening for all patients with DLBCL. An additional PET scan in DLBCL patients should be obtained at the 6-month tumor assessment to ensure consistency of response assessment methodology at this time point for all patients. PET scans should additionally be

obtained to confirm disappearance of metabolically active disease during study treatment and to confirm a complete response (CR) upon discontinuation of study treatment.

For patients with FL, PET scans are not required but may be obtained based on physician preference and if permitted by local health authorities. Similar for DLBCL, PET scans on FL patients should be obtained during screening; for patients whose tumors are PET-positive during screening, an additional PET scan should be obtained at the 6-month tumor assessment. PET scans should additionally be obtained to confirm disappearance of metabolically active disease during study treatment and to confirm a complete response (CR) upon discontinuation of study treatment.

For all patients regardless of disease subtype, combined PET-CT scans may be used instead of CT alone if performed with contrast and if collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent PET-CT scans. If a PET-CT scan is to be used during screening, then PET-CT scans should be performed for all subsequent tumor assessments in order to ensure their consistency across different timepoints.

All tumor assessments will be submitted to an independent review facility (IRF) for storage and possible independent centralized review. Details related to submission of data to the IRF will be defined in a separate Imaging Manual.

b. Bone Marrow Assessments

A bone marrow biopsy for morphology is required at screening and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated.

c. Schedule of Tumor Response Assessments

Tumor response assessments will be performed every three months (± 1 week) from the initiation of study treatment until study treatment completion or early termination, e.g., between Days 14 and 21 of Cycles 4 and 8 for those patients receiving at least eight 21-day cycles of treatment. The schedule of tumor assessments should be independent of the study treatment dose schedule. The schedule of tumor response assessments is detailed in Appendix A-1. As stated above, for all DLBCL patients, PET scans are required during the screening period and at the 6-month tumor assessment timepoint.

The schedule for tumor response assessments for patients who proceed to crossover treatment is detailed in Appendix A-2.

Additional response assessments, after the final dose of study treatment, for patients who discontinue from study treatment (either initial or crossover treatment) for reasons other than progressive disease, will be performed as described in Appendix A-3.

Tumor assessments should also be performed within 30 days after the last study drug infusion (both initial and crossover treatment) at the treatment completion/early termination visit. Imaging scans are not required at the treatment completion/early termination visit if scans have been performed within the previous 8 weeks or if disease progression while receiving study treatment is documented..

If at any time during the study disease progression is suspected, a tumor assessment must be performed.

4.5.1.9 Exploratory Research

a. Tumor Tissue Samples

Required Tumor Tissue Samples

Tumor tissue samples will be used for central pathologic laboratory review of CD20, CD22 and CD79b expression. Additional studies to fulfill the exploratory objectives in Section 3.3.4 will be performed, including but not limited to the following:

- Messenger RNA (mRNA) expression profiling for signatures of NHL biology, including prognostic subpopulations (Alizadeh et al. 2000; Wright et al. 2003), target expression (CD20, CD22 and CD79b) and apoptotic response
- Tissue microarrays (TMAs) from cores taken from provided blocks for IHC and ISH assessments, including: 1) DLBCL classifiers in tissue obtained from patients with DLBCL (CD10; GCET, Mum1; FoxP1 LMO2 (Meyer P N et al. 2011); and 2) biomarker endpoints involved in response to chemotherapy including quantitation of Bcl-2 protein and genetic alterations of bcl-2 including gene rearrangements, amplifications and t(14;18) translocations. Additional IHC markers may include those related to the tumor microenvironment.
- Tumor DNA to assess mutations that have been shown to be associated with NHL biology and activation of the B-cell receptor, including mutations in CD79b (Pasqualucci et al. 2012)

For patients who develop progressive disease and are eligible to receive crossover treatment (see Section 3.1.3) a biopsy of a safely accessible site of disease will be performed. Tumor tissue samples obtained at this time point will be used to assess changes in biology, target expression and regulators of apoptosis as described above, which have occurred and may be linked to progression on initial study treatment.

Optional Tumor Tissue Samples (Requires Optional Research Informed Consent

For patients who provide informed consent, an optional tumor biopsy will be collected at time of progression from the following patients:

- Patients who develop disease progression following initial study treatment and do not proceed to receive crossover treatment
- Patients who develop disease progression on crossover treatment

Tumor tissue samples obtained at these time points will be used to assess changes in biology, target expression and regulators of apoptosis, as described above, that have occurred and may be linked to progression on treatment.

b. Blood and Plasma Samples

A plasma sample will be collected prior to treatment.

For patients who sign the Optional Research Informed Consent, an additional blood sample will also be taken prior to treatment.

The plasma and blood samples may be used for the assessment of specific tumor biologic markers, including proteins, circulating DNA, and microRNAs. The information obtained from these samples will enable a better understanding of the biology of NHL and disease prognosis, identify potential predictors of response to treatment with DCDT2980S, DCDS4501A and/or rituximab, improve diagnostic assessments, and identify and characterize mechanisms of resistance to DCDT2980S or DCDS4501A and rituximab activity.

As tumorigenesis is a multiple step process linked to somatic events, any DNA analysis will focus on sporadic mutations specifically found in tumor tissue and not on inherited changes found in the whole body. For this purpose, some tumor-containing sections may be taken from the tissue block and used for the DNA extraction process. Assays on stored tissue samples may be performed at Genentech or at a central specialty laboratory.

4.5.1.10 Patient Reported Outcome

The M.D. Anderson Symptom Inventory (MDASI; Cleeland et al., 2000; Appendix E) is a multi-symptom patient-reported outcome (PRO) measure for clinical and research use. The MDASI's 13 core symptom items, plus an additional four items for a total of 17 symptom items, include those found to have the highest frequency and/or severity in patients with various cancers and treatment types. These include pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering and numbness or tingling. Six additional items focus on the degree of interference of the aforementioned symptoms for a total of 23 items in the questionnaire.

Patient-reported outcome data will be elicited from all patients in this study to more fully characterize the clinical profile of study treatment. The MDASI PRO instrument will be supplied in the local language of each participating country. Electronic (hand held computers) will be used for the daily collection of symptoms derived from the MDASI.

4.5.2 Screening and Pretreatment Assessments

All screening evaluations must be completed and reviewed by the Genentech Medical Monitor or designated CRO Medical Monitor to confirm that patients meet all eligibility criteria and are approved for enrollment before the first infusion of study treatment. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site.

Screening and pretreatment tests and evaluations will be performed within 28 days preceding the day of the first dose of study treatment on Cycle 1 Day 1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 may be used; such tests do not need to be repeated for screening.

The availability of a patient's tumor tissue sample for studies (see Sections 4.1.1 and 4.5.1.i) should be confirmed prior to Cycle 1, Day 1. Such specimens should consist of representative core biopsy in a paraffin block, which is the preferred method, or at least 15 unstained slides. Tumor specimens should be submitted with an accompanying pathology report and may be obtained at any time prior to entry to study.

Bone marrow biopsy and aspirate specimens are required at screening (see Section 4.5.1.8). Unsuccessful attempts at obtaining marrow aspirates will not be considered a protocol deviation or violation.

Refer to the Study Flowchart provided in Appendix A-1 for the schedule of screening and pretreatment assessments.

4.5.3 Assessments during Treatment

Study drug infusions (rituximab, DCDT2980S or DCDS4501A) should occur on the scheduled 21-day (or 28-day) cycle, but may be given up to $\pm$ 2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within $\pm$ 1 day from the scheduled date, unless otherwise noted. Study visits starting in Cycle 3 should occur within $\pm$ 2 days from the scheduled date, unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed prior to study drug infusion unless otherwise noted.

Local laboratory assessments may be performed within 72 hours preceding study drug administration on Day 1 of each cycle. Otherwise, laboratory samples should be drawn 0–4 hours pre-infusion. Results must be reviewed and the review documented prior to study drug administration.

Refer to the Study Flowchart provided in Appendix A-1 for the schedule of treatment period assessments.

4.5.4 Study treatment Completion Visit

Patients who complete study treatment (approximately 1 year/17 cycles) or discontinue from study treatment early will be asked to return to the clinic within 30 days after the last DCDT2980S or DCDS4501A or rituximab infusion (whichever is later) for a study treatment completion visit. The visit at which response assessment shows progressive disease may be used as the early termination visit.

Refer to the Study Flowchart provided in Appendix A-1 for assessments to be performed at the treatment completion/early termination visit.

Assessments conducted at the treatment completion/early termination visit may be used for the purposes of re-screening to determine eligibility to receive crossover treatment (see Section 3.1.3 and Section 4.5.5).

4.5.5 Crossover Treatment Completion Visit

Patients who fulfill the criteria to receive crossover treatment (see Section 3.1.3) will have assessments during the crossover treatment period as described in Appendix A-2. The same guidelines regarding scheduling of assessments for treatment with initial study treatment as detailed in Section 4.5.3 will apply to crossover treatment.

Patients who proceed to receive crossover treatment will have on-treatment assessments as described in Appendix A-2.

Patients who complete the crossover treatment (approximately 1 year/17 cycles) or discontinue from crossover treatment early will be asked to return to the clinic within 30 days after the last DCDT2980S, DCDS4501A or rituximab infusion (whichever is later) for a crossover treatment completion/early termination visit. The visit at which response assessment shows disease progression on crossover treatment may be used as the early termination visit.

Refer to Appendix A-2 for assessments to be performed at the treatment completion/early termination visit.

4.5.6 Follow-Up Assessments

Ongoing adverse events thought to be related to DCDT2980S, DCS4501A, or rituximab will be followed until the event has resolved to baseline (pre-treatment) grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the adverse event.

Patients will be followed after the last dose of study treatment (either initial study treatment or crossover treatment) for safety outcomes. Such follow-up will require an assessment (per verbal report, at minimum) of any adverse events and serious adverse events for 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy, whichever occurs first.

Patients who discontinue from study treatment (either initial study treatment or crossover treatment) for reasons other than progressive disease will be followed for response for up to 1 year after the last infusion of study treatment or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Response assessments should occur approximately every 2–3 months following the last infusions of DCDT2980S, DCDS4501A or rituximab. Post-treatment assessments are described in Appendix A-3.

Following discontinuation of study treatment, patients will be followed for survival approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.

4.6 PATIENT DISCONTINUATION

4.6.1 Discontinuation from Treatment

Patients may discontinue study treatment early for reasons other than disease progression, such as patient/investigator choice or unacceptable toxicity. The reasons for early discontinuation of treatment must be documented on the appropriate eCRF. Patients may continue treatment with either DCDT2980S/DCDS4501A or rituximab alone following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor

Patients who discontinue study treatment early due to toxicity should continue to be followed until resolution of toxicity as scheduled.

Refer to Sections 4.5.4 and 4.5.5 for assessments that are to be performed for patients who discontinue from the study during the study treatment period.

4.6.2 Discontinuation from Study

Patients must be discontinued from the study if they experience disease progression as defined using response and progression criteria in Appendix C. Patients can continue crossover treatment following documentation of the first progressive disease event but must be discontinued from the study if they experience a second progressive disease event on the crossover treatment.

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study, for reasons of noncompliance (e.g., missed doses, visits), pregnancy, or if the investigator determines it is in the best interest of the patient.

Refer to Section 4.5.4 and 4.5.5 for assessments that are to be performed for patients who prematurely discontinue from the study during the treatment period.

4.7 STUDY DISCONTINUATION

Genentech has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

4.8 POST-TRIAL ACCESS

Genentech does not have any plans to provide DCDT2980S, DCDS4501A, rituximab or other study interventions to patients after the conclusion of the study or the study is terminated, or for patients who withdraw early from the study or complete their study treatment. Genentech will evaluate the appropriateness of continuing to provide DCDT2980S, DCDS4501A, or rituximab to study patients after evaluating the safety and activity data from the study.

4.9 ASSAY METHODS

4.9.1 Total DCDT2980S/DCDS4501A Antibody ELISA

Total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) will be measured in serum samples using validated ELISAs.

4.9.2 Antibody-Conjugated MMAE (MMAE Affinity Capture Enzyme-Release LC/MS-MS)

Antibody-conjugated MMAE (a measure of MMAE conjugated to DCDT2980S/DCDS4501A) will be measured in plasma samples using validated affinity capture enzyme-release LC-MS/MS assays.

4.9.3 Free MMAE LC-MS/MS

Free MMAE will be measured in plasma samples using a validated electrospray LC-MS/MS method.

4.9.4 Rituximab ELISA

Rituximab will be measured in serum samples using a validated ELISA.

4.9.5 Anti-Therapeutic Antibody

ATAs against DCDT2980S and DCDS4501A in serum samples will be measured using validated bridging antibody ELISAs and characterized by competitive binding assays.

4.9.6 Biomarker Assays

Tumor tissue assessment of biomarkers will be assayed using IHC; *in situ* hybridization (ISH), qPCR gene expression profiling using microarray, mutation detection assays and flow cytometry.

4.10 STATISTICAL METHODS

The final analysis will be based on patient data collected through patient discontinuation or study discontinuation, whichever occurs first. The analyses will be based on the safety evaluable population defined as patients who received at least one dose of study treatment. All summaries will be presented according to the *disease specific cohort, treatment group, and assigned dose level.*

4.10.1 Analysis of the Conduct of the Study

Enrollment, major protocol violations, and reasons for discontinuations from the study will be summarized.

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, duration of malignancy, and baseline ECOG Performance Status, will be summarized using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables. All summaries will be presented overall and by treatment group*, assigned dose level,* and disease-specific cohort.

Study drug administration data will be listed by the disease-specific cohorts described in Section 3.1.1 and 3.1.2. Any dose modifications will be flagged. Means and standard deviations will be used to summarize the total doses of DCDT2980S, DCDS4501A and rituximab received. All summaries will be presented by treatment group*, assigned dose level,* and disease-specific cohort.

4.10.2 Safety Analysis

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in physical findings on physical examinations, and changes in vital signs. All patients who receive any amount of DCDT2980S, DCDS4501A or rituximab

will be included in the safety analysis and will be assigned to the treatment *group* based on the study treatment received. *Patients who have dose level changes from the initial assigned dose level will be summarized by the initial assigned dose level of DCDT2980S or DCDS4501A.*

All adverse event data will be listed by study site, patient number, treatment group, disease-specific cohort, and cycle. All adverse events occurring on or after treatment on Day 1 of Cycle 1 will be summarized by mapped terms, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade. In addition, all serious adverse events, including deaths will be listed separately and summarized.

Selected laboratory data will be listed, with values outside of normal ranges identified. The incidence of antibodies to DCDT2980S and DCDS4501A will be summarized.

4.10.3 Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum concentrations of total DCDT2980S or DCDS4501A antibody (conjugated and unconjugated antibody) and rituximab, and plasma concentrations of antibody-conjugated MMAE and free MMAE versus time data will be tabulated and plotted by NHL disease subtype (relapsed/refractory follicular NHL or DLBCL). The pharmacokinetics of the above analytes will be summarized by estimating the appropriate PK parameters (e.g., AUC, C_{max}, CL, V_{ss}, and $t_{1/2}$). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and range). Non-compartmental, compartmental and/or population methods will be used, as data allow.

Exposure-response (safety and efficacy) analysis may be conducted using PK data and available drug effect (e.g., imaging, measures of tumor burden), and toxicity (e.g., clinical pathology) data, at the sponsor's discretion.

In addition, population PK methods may be employed to manage sparse data and to investigate the effects of certain covariates on the pharmacokinetics of DCDT2980S and DCDS4501A, as data allow, and at the sponsor's discretion.

4.10.4 Activity Analyses

Best overall response, duration of response, and PFS will be listed for all patients.

Objective response rate from the initial study treatment will be calculated based on data from patients who received study treatment and had at least one post-baseline response assessment. Objective response is defined as complete response (CR) or partial response (PR) as determined by the investigator, based on physical examinations, radiographic scans, and bone marrow examinations, using modified response criteria for NHL (Cheson et al. 2007; see Appendix C), and confirmed by repeat assessments $\geq$4 weeks after initial documentation. Any patient with insufficient data to determine response will be classified as a non-responder.

For patients with DLBCL, primary assessment of tumor response will be based on diagnostic imaging scans, e.g., CT and/or MRI, and PET scans. For patients with FL, primary assessment of response will be based on CT scans only; the assessment of response in FL based on PET scans will be performed for exploratory purposes only.

Among patients with an objective response, duration of response will be defined as the time from the initial CR or PR to the time of disease progression or death. If a patient does not experience death or disease progression before the end of the study, duration of response will be censored at the day of the last tumor assessment.

For the randomized portion of the study (Arms A and B), PFS is defined as the time from the date of randomization to the date of disease progression or death *from any cause*, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the day of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. *For the nonrandomized portion of the study (Cohorts C and D), PFS is defined as the time from the date of study enrollment to the date of disease progression or death from any cause, whichever occurs first.*

*For the randomized portion of the study (Arms A and B), o*verall survival is defined as the time from the date of randomization to the date of death from any cause. *For the nonrandomized portion of the study (Cohorts C and D), overall survival is defined as the time from the date of study enrollment to date of death from any cause.*

4.10.5 Exploratory Analyses

Assay results of possible predictive markers will be listed by treatment group and response status.

Summary statistics of the MDASI items, scales, and their changes from baseline will be calculated at each assessment timepoint. The mean, standard error, and median of the absolute scores and the mean changes from baseline (and 95% CI) within and between study arms will be reported for the MDASI scales and single items, as well as the weekly averages of the worst symptom rating. For change scores in the MDASI from baseline, patients without baseline scores will not be included in the analyses. Line charts depicting the means and mean changes of subscales over time will be also provided.

Frequencies and percentages of missing data for the patient-reported outcome endpoints will be reported. Dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) will be summarized.

Repeated measures mixed-effects models will explore MDASI subscale scores with a baseline score and appropriate covariates added, as appropriate.

4.10.6 Handling of Missing Data

For the endpoint of objective response, patients without a post-baseline tumor assessment will be considered non-responders in the all-treated population analysis.

For duration of response and PFS, data from patients who are lost to follow-up will be included in the analysis as censored observations on the last date that the patient is known to be progression free, defined as the date of the last tumor assessment, or, if no tumor assessments were performed, as the date of last study treatment plus 1 day.

Compliance to PRO data collection will be reported with summary statistics, including frequencies of reasons for non-compliance such as patient refusal to complete PRO data collection.

4.10.7 Determination of Sample Size

For the randomized portion of the study (Arms A and B), a target of 120 patients will be enrolled in two separate cohorts of patients (40 in the follicular NHL cohort and 80 in the DLBCL cohort). Genentech has judged this sample size to provide sufficient precision in estimating the anti-tumor activity of DCDT2980S combined with rituximab or DCDS4501A combined with rituximab as measured by objective response. For example, with the assumption of an observed response rate of 40%, a 90% confidence interval for the response rate would be approximately 22%–58% (i.e., 40% $\pm$ 18%) for the follicular NHL cohort and approximately 27%–53% (i.e., 40% $\pm$ 13%) for the DLBCL cohort.

This is a non-comparative hypothesis-generating study. There is no formal hypothesis testing planned to compare the treatment arms. *Specifically, for the randomized portion of the study,* there is insufficient power to detect minimum clinically meaningful differences between the two treatment arms.

4.11 DATA QUALITY ASSURANCE

The data will be collected via Electronic Data Capture (EDC) using eCRFs. The site will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The CRO will be responsible for the data management of this trial, including quality checking of the data.

Genentech will perform oversight of the data management of this trial. Genentech will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central Laboratory data and other electronic data will be sent directly to Genentech, using Genentech's standard procedures to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Genentech and records retention for the study data will be consistent with Genentech's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; physical examinations and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

Genentech or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Genentech or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Genentech or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/ECs (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

5.1.1 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the baseline hematologic malignancy (i.e., leukemia or lymphoma) that were not present prior to the AE reporting period (see Section 5.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., medication washout, no treatment run-in, or invasive procedures such as biopsies)
- Preexisting medical conditions other than the disease under study that are judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

5.1.2 Serious Adverse Event

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the investigator (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

5.1.3 *Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)*

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions), irrespective of regulatory seriousness criteria. Adverse events of special interest for this study include the following:

- *Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.1.6; treatment-emergent ALT or AST >3 ×baseline value in combination with total bilirubin >2 ×ULN [of which 35% is direct bilirubin])*
- *Suspected transmission of an infectious agent by the study drug*
- *Grade ≥2 motor neuropathy*
- *Grade ≥2 infusion reactions*

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 5.1) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

5.2.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

After initiation of study drug (the Genentech product(s) or other investigational medicinal product), all new AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see Section 5.6).

5.2.2 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.2.3 Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity and causality.

Table 2 provides guidance for grading AE severity and Table 3 provides guidance for assessing the causal relationship to the investigational product(s).

The AE grading (severity) scale found in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 will be used for AE reporting.

Table 2 Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Transient or mild discomfort (<48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

AE=adverse event; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; SAE=serious adverse event.

The NCI CTCAE v4.0 can be found: http://ctep.cancer.gov/reporting/ctc_v30.html

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE (see Section 5.1.2).

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.

To ensure consistency of causality assessments, investigators should apply the following general guidelines:

Table 3 Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

AE=adverse event; SAE=serious adverse event.

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

5.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

5.3.1 Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF. Avoid colloquialisms and abbreviations.

There is one eCRF page for recording AEs or SAEs.

Only one medical concept should be recorded in the event field on the Adverse Event eCRF.

5.3.1.1 Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

5.3.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

5.3.1.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF.

5.3.1.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management, e.g., concomitant medication, will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.)

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Specific to this study, lymphopenia and leukopenia due to lymphopenia of any grade are expected PD effects of study drug and therefore are not considered to be adverse events. However, complications of lymphopenia (e.g., infections) will need to be reported as adverse events. In addition, because monocytopenia is not reportable and neutropenia is already being monitored and reported as an adverse event, leukopenia does not need to be reported as a distinct adverse event.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

5.3.1.5 *Abnormal Vital Sign Values*

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- *Accompanied by clinical symptoms*
- *Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)*
- *Results in a medical intervention (including a diagnostic evaluation not mandated in this protocol) or a change in concomitant therapy*
- *Clinically significant in the investigator's judgment*

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.1.6 *Abnormal Liver Function Tests*

The finding of an elevated ALT or AST (>3 ×baseline value) in combination with either an elevated total bilirubin (>2 ×ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- *Treatment-emergent ALT or AST >3 ×baseline value in combination with total bilirubin >2 ×ULN (of which 35% is direct bilirubin)*
- *Treatment-emergent ALT or AST >3 ×baseline value in combination with clinical jaundice*

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2)

5.3.1.7 Deaths

Deaths that occur during the protocol-specified AE reporting period (see Section 5.2.1) that are attributed by the investigator solely to progression of lymphoma will be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of attribution, will be recorded on the Adverse Event eCRF and expeditiously reported to the Sponsor.

When recording a death on an eCRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” on the Adverse Event eCRF.

5.3.1.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History eCRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When

recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.1.9 Worsening of Baseline Hematologic Malignancy

Worsening and/or progression of the baseline hematologic malignancy (e.g. leukemia or lymphoma) should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

5.3.1.10 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

5.3.1.11 Pregnancy

If a female patient becomes pregnant while receiving the study drug or within 6 months after the last dose of investigational product, a Pregnancy Report eCRF should be completed within 24 hours of learning of the pregnancy. A pregnancy report will automatically be generated and sent to Genentech's Drug Safety Department or its designee. Pregnancy should not be recorded on the Adverse Event eCRF.

Male patients must also be instructed to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study drug. If such an event occurs, it should be reported as described below.

Abortion, whether therapeutic or spontaneous, should always be classified as an SAE (as the Sponsor considers these medically significant), recorded on an Adverse Event eCRF, and expeditiously reported to the Sponsor (see Section 5.4.2).

Any congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and expeditiously reported to the Sponsor (see Section 5.4.2).

After the study period, abortions, congenital anomalies/birth defects, and pregnancy outcomes should still be reported expeditiously to the Sponsor.

In the event the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee within 24 hours of learning of the pregnancy, at the fax numbers listed in Section 5.4.2.

a. Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 1 working day after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee within 24 hours of learning of the pregnancy, at the fax numbers listed in Section 5.4.2.

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

5.4.1 Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an eCRF within 24 hours as described in Section 5.4.2.

Medical Monitor Contact Information for sites in North America:

Medical Monitor:	[redacted] M.D.
Telephone No.:	[redacted]
Alternate Telephone No.:	+1 (888) 835-2555 (US sites only)

For sites outside of North America, local contact details and numbers for safety issues and safety reporting will be provided in the study reference binder.

5.4.2 *Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest*

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to the Sponsor's Safety Risk Management department by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Sites in North America:

Fax No.: [redacted]

Alternate Fax No.: [redacted]

Sites outside of North America: Refer to the study reference binder for contact information.

Relevant follow-up information should be submitted to Genentech's Drug Safety Department or its designee as soon as it becomes available and/or upon request

5.5 TYPE AND DURATION OF FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV).

For some SAEs, the Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

5.6 POST-STUDY ADVERSE EVENTS

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt to be related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to Genentech Drug Safety on the study eCRF. If the study eCRF is no longer available, the investigator should report the event directly to Genentech Drug Safety via phone at 1-888-835-2555.

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with Genentech or a Genentech representative:

- U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

  The names of any subinvestigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae and evidence of licensure of the Principal Investigator and all subinvestigators
- Complete financial disclosure forms for the Principal Investigator and all subinvestigators listed on the U.S. FDA Form 1572
- Federalwide Assurance number or IRB statement of compliance
- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form

  Genentech or its designee must review any proposed deviations from the sample Informed Consent Form.
- Current laboratory certification of the laboratory performing the analysis (if other than a Genentech-approved central laboratory), as well as current references ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator Brochure Receipt signed and dated by the Principal Investigator
- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable) , IRB/EC approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator

- Canada only when applicable: original Qualified Investigator Undertaking Form, signed by each Canadian investigator involved in the study
- For global studies, list documents as appropriate for additional countries.

6.2 STUDY COMPLETION

The following data and materials are required by Genentech before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- All laboratory certifications for laboratories performing the analysis (is other than Genentech-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and subinvestigator, U.S. FDA Form 1572 for each site)
- A signed and dated Protocol Amendment Acceptance Form(s) [if applicable]
- Updated financial disclosure forms for the Principal Investigator and all subinvestigators listed on the U.S. FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

6.3 INFORMED CONSENT FORM

Genentech's Sample Informed Consent Form will be provided to each site. Genentech or its designee must review and approve any proposed deviations from the Sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the Consent Forms during their participation in the study. The final IRB/EC-approved Consent Forms must be provided to Genentech for regulatory purposes.

The Consent Forms must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved Informed Consent Form must be provided to Genentech for regulatory purposes.

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval, and other processes outlined above apply except that IRB/IEC review and approval may not be required per study site policies.

Optional Research Informed Consent

Informed consent for the collection and use of fresh tumor tissue at time of progression for optional research described in Section 4.5.1.10 will be documented in a section of the main Informed Consent Form. This section provides patients with the option to authorize the collection and use of these samples and personal health information for additional research purposes. Agreement to participate in the optional research (by checking the appropriate box in this section of the main Informed Consent Form) is not required for enrollment in the trial but is required prior to any optional research sample collection. Optional consent may be withdrawn at any time by the patient.

6.4 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from Genentech. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's Study File.

6.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Genentech representative to inspect study data, patients' medical records, and eCRFs. The Principal Investigator will permit Genentech monitors/representatives and collaborators, the U.S. FDA, other regulatory agencies, Institutional Review Boards, and the respective national or local health authorities to inspect facilities and records relevant to this study.

6.6 ELECTRONIC CASE REPORT FORMS

eCRFS are to be completed using the [redacted] EDC system. Sites will receive training for appropriate eCRF completion. eCRFs will be submitted electronically to Genentech and should be handled in accordance with instructions from Genentech.

All eCRFs should be completed by designated, trained personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

In addition, at the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

6.7 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing SDV to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

6.8 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

In collaboration with the study monitor, Genentech's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

6.9 STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by Genentech. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Genentech with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

6.10 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

6.11 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of Genentech. Written notification should be provided to Genentech for transfer of any records to another party or moving them to another location.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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Appendix A-1
Study Flowchart: Initial Study Treatment

Cycle	Screening	Treatment Period											Treatment Completion/ Early Termination Visit [c]	Safety *and Survival* Follow-Up [d]
		Cycle 1				Cycles 2–4				Cycles 5–17				
Day(s)[a] Assessment	−28 to −1	1[b]	2	8	15	1[b]	2	8	15	1[b]	2	15		
Written informed consent [e]	x													
Review inclusion/exclusion criteria	x													
Medical history and demographics	x													
Height (screening only) and weight	x	x				x				x				
Vital signs	x	x[f]	x[f]	x	x	x[f]	(x)[f]	x	x	x[f]	(x)[f]	x	x	
ECOG Performance Status	x	x		x	x	x		x	x	x			x	
B symptoms [g]	x	x				x				x			x	
Complete physical examination [h]	x													
Targeted physical examination [i]		x	x	x		x	(x)			x	(x)		x	
Concomitant medications	x	x	x	x	x	x	(x)	x	x	x	(x)	x	x	
Adverse events [j]	x	x	x	x	x	x	(x)	x	x	x	(x)	x	x	x
MDASI PRO [k]		Day 1–8 of Cycles 1–8												
12-lead electrocardiogram [l]	x	Refer to Footnote “l”											x	
Tumor assessments [m]	x	Every 3 months											x	
PET scan (required for DLBCL; optional for FL) [m]	x	6-month tumor assessment and as clinically indicated												
Rituximab infusion		x				x				x				
DCDT2980S or DCDS4501A infusion [n]			x			x	(x)			x	(x)			

Appendix A-1 (cont.)
Study Flowchart: Initial Study Treatment

Cycle	Screening	Treatment Period											Treatment Completion/ Early Termination Visit [c]	Safety *and Survival* Follow-Up [d]
		Cycle 1				Cycles 2–4				Cycles 5–17				
Day(s)[a] Assessment	−28 to −1	1[b]	2	8	15	1[b]	2	8	15	1[b]	2	15		
Local Laboratory Assessments														
HBV and HCV screening [o]	x													
Hematology [p]	x	x		x	x	x		x	x	x		x	x	
Serum chemistry [q]	x	x		x	x	x		x	x	x		x	x	
Hemoglobin A1c	x									Cycle 5 Day 1				
Total IgA, IgG, IgM	x									Cycle 8 Day 1			x	
Coagulation (aPTT, PT, and INR)	x													
Pregnancy test [r]	x	Within 10 days of Day 1 of Cycles 3, 6, 9, 12, and 15											x	
Bone marrow biopsy [s]	x	Perform to confirm CR if positive for disease at screening or if clinically indicated												
Central Laboratory Assessments														
Leukocyte immunophenotyping (FACS) [t]		Day 1 of Cycle1, Cycle 4, Cycle 8 and Cycle12											x	
Tumor tissue sample [u]	x												x	
Exploratory plasma (required) and blood (optional) sample [v]	x													
DCDT2980S or DCDS4501A and rituximab pharmacokinetic sampling [w]	Refer to Appendix B													
Serum sample for anti-DCDT2980S or anti-DCDS4501A antibody [x]														

Appendix A-1 (cont.)
Study Flowchart: Initial Study Treatment

aPTT = activated partial thromboplastin time; AE = adverse event; CR = completed response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorter; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalized ratio; MDASI: MD Anderson Symptom Inventory; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography; PT = prothrombin time; QLQ = Quality of Life Questionnaire; SAE = serious adverse event; (x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle —refer to footnote 'n' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 1 year (approximately 17 cycles on an every-21-day schedule) and may be given up to ±2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ± 1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 3 should occur within ± 2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DCDT2980S or DSDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 1 year of total study treatment (approximately 13 cycles).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding rituximab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] Perform within 30 days after the last infusion of DCDT2980S, DCDS4501A, or rituximab. The visit at which response assessment shows progressive disease may be used as the early termination visit. Assessments during the treatment completion/early termination visit may be applied to assessments required to determine eligibility to receive crossover treatment. *Patients enrolled into Cohorts C and D are not eligible to receive crossover treatment.*

[d] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report from the patient, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-3 for schedule of assessments during the post-treatment period. *Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.*

[e] Informed consent form(s) must be signed by the patient before any study-specific procedures are performed.

[f] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2 of the protocol.

[g] Defined as unexplained weight loss >10% over previous 6 months, fever (>38°C/100.4°F), and/or drenching night sweats.

[h] Complete physical examination includes all systems described in Section 4.5.1.3.

[i] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDT2980S or DCDS4501A dosing on Day 2 of each cycle if given on separate days from rituximab only if clinically indicated, e.g. to follow- up on signs or symptoms observed from the examinations performed on Day 1.

[j] After informed consent is obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs and SAEs, regardless of attribution, must be reported until 30 days following the last administration of study drug or until the patient receives another anti-cancer therapy, whichever occurs first. After this period, investigators should report only SAEs considered related to prior study treatment.

[k] Treatment and disease associated symptoms using the MDASI questionnaire will be collected on hand-held computer devices (see Section 4.5.1.10).

[l] Twelve-lead digital electrocardiogram (ECG) measurements must be obtained in triplicate (with immediately consecutive ECGs obtained until three evaluable ECGs are recorded) at the time points specified in Section 4.5.1.5. Non-triplicate ECGs should also be performed when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction. The evaluating physician should determine the clinical significance of any abnormal ECGs.

[m] Tumor assessments should be performed at screening and every 3 months while receiving study treatment regardless of study treatment dose schedule. Tumor assessments should also be performed within 30 days after the last study drug infusion as part of the treatment completion/early termination visit. Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C). For DLBCL patients, a PET scan is required during screening, at the 6-month tumor assessment timepoint and as clinically indicated. For FL patients, a PET scan is not required but may be obtained based on physician preference and if permitted by local health authorities. Refer to Section 4.5.1.8 for complete details.

[n] Administer DCDT2980S or DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related adverse events. For Cycle 1 and Cycle 2, DCDT2980S or DCDS4501A should be administered on the day after rituximab is administered, e.g. Day 2 if rituximab is given on Day 1, or Day 3 if rituximab is given as a split dose on Days 1 and 2. In the absence of any infusion-related adverse events, rituximab followed by DCDT2980S or DCDS4501A may be administered on the same day in each cycle starting with Cycle 3. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle, but may be given up to ± 2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[o] HBsAg, HBcAb, and Hep C Ab serology required. If HBcAb or HCV antibody is positive, HBV / HCV DNA by PCR is required.

[p] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[q] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), and uric acid. Serum gamma-glutamyl transpeptidase (GGT) levels will be required at screening only.

[r] A serum pregnancy test should be performed for women of childbearing potential performed within 14 days prior to receiving first study treatment. In addition, a urine pregnancy test must also be performed within 10 days prior to Day 1 of Cycles 3, 6, 9, 12, and 15, and at the treatment completion/early termination visit unless patient receives crossover treatment, in which case follow the schedule of pregnancy testing outlined in Appendix A-2. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[s] Bone marrow biopsy for morphology (aspirates for morphology and/or flow studies are optional) is required at screening. Bone marrow biopsy for morphology are required at screening and should reflect disease status in the bone marrow following documented relapse on the last prior therapy or within 3 months of Day 1, whichever occurs later. If the bone marrow biopsy at screening demonstrates presence of tumor cells, a subsequent bone marrow examination is required only to confirm a CR or if clinically indicated. If the bone marrow biopsy at screening does not demonstrate presence of tumor cells, then subsequent bone marrow examination is required only if clinically indicated. Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.

[t] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[u] Availability of archival or freshly biopsied tumor tissue samples should be confirmed at screening. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, obtained at any time prior to entry to study. A biopsy of a safely accessible site of disease, defined as requiring only local anesthesia and in general excluding brain, lungs or any internal organs that may subject patients to significant risk, is required for patients who proceed to crossover treatment; if no such lesion exists then a biopsy is not required.

[v] All patients who have successfully passed screening and are fully eligible for the study will have a 10-mL plasma sample taken for exploratory research.

[w] Pharmacokinetic serum and plasma samples should be drawn according to the schedule provided in Appendices B-1 and B-2.

[x] Whole blood samples for assessment of anti-DCDT2980S or anti-DCDS4501A antibodies in serum will be drawn according to the schedule provided in Appendices B-1 and B-2.

Appendix A-2
Study Flowchart: Crossover Treatment *(Patients Randomized to Arms A or B Only)*

Cycle	Treatment Period											Crossover Treatment Completion/Early Termination Visit [c]	Safety *and Survival* Follow-Up [d]
	Cycle 1b				Cycles 2b–4b				Cycles 5b–17b				
Day(s) [a] Assessment	1 [b]	2	8	15	1 [b]	2	8	15	1 [b]	2	15		
Weight	x				x				x				
Vital signs	x [e]	(x) [e]	x	x	x [e]	(x) [e]	x	x	x [e]	(x) [e]	x	x	
ECOG Performance Status	x		x	x	x		x	x	x			x	
B symptoms [f]	x				x				x			x	
Targeted physical examination [g]	x	(x)	x		x	(x)			x	(x)		x	
Concomitant medications	x	(x)	x	x	x	(x)	x	x	x	(x)	x	x	
Adverse events [h]	x	(x)	x	x	x	(x)	x	x	x	(x)	x	x	x
Tumor assessments [i]	Every 3 months											x	
Rituximab infusion	x				x				x				
DCDT2980S or DCDS4501A infusion [j]	x	(x)			x	(x)			x	(x)			
Local Laboratory Assessments													
Hematology [k]	x		x	x	x		x	x	x		x	x	
Serum chemistry [l]	x		x	x	x		x	x	x		x	x	
Total IgA, IgG, IgM									Cycle 8b Day 1			x	
Pregnancy test [m]	Day 1 of Cycles 3b, 6b, 9b, 12b, and 15b											x	
Bone marrow biopsy [n]	Perform to confirm CR if positive for disease at screening or if clinically indicated												
Central Laboratory Assessments													
Leukocyte immunophenotyping (FACS) [o]	Day 1 of Cycle 4, 8, and 12											x	
Tumor biopsy/sample												x [p]	

Appendix A-2 (cont.)
Study Flowchart: Crossover Treatment *(Patients Randomized to Arms A or B Only)*

(x) = Assessment or action to be performed only if study treatment is administered on Day 2 of the Cycle—refer to footnote 'j' for details.

[a] Study drug infusions should occur on the scheduled 21-day cycle up to a maximum of 1 year (approximately 17 cycles) and may be given up to ± 2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. All other study visits during Cycles 1 and 2 must occur within ± 1 day from the scheduled date unless otherwise noted. Study visits starting in Cycle 3 should occur within ± 2 days from the scheduled date unless otherwise noted. Treatment cycles may be extended to 28 days if needed to provide sufficient time for recovery from a transient and reversible toxicity (e.g., cytopenia) without reducing the dose of DCDT2980S or DSDA4501A. Patients receiving study treatment on 28-day cycles should also follow the assessment schedule above up to a maximum of 1 year of total study treatment (approximately 13 cycles).

[b] Local laboratory assessments and targeted physical examination may be performed within 72 hours preceding rituximab administration unless otherwise specified; pre-infusion laboratory samples should be drawn 0–4 hours prior to infusion.

[c] Perform within 30 days after the last infusion of DCDT2980S, DCDS4501A or rituximab. The visit at which response assessment shows progressive disease may be used as the early termination visit.

[d] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-3 for schedule of assessments during the post-treatment period. *Patients will also be followed for survival following study treatment discontinuation approximately every three months until death, loss to follow-up, withdrawal of consent, or study termination.*

[e] Vital signs on days of study treatment administration should be recorded according to Section 4.5.1.2 of the protocol.

[f] Defined as unexplained weight loss > 10% over previous 6 months, fever (> 38°C/100.4°F), and/or drenching night sweats.

[g] Targeted physical examinations should be limited to systems of clinical relevance and those systems associated with clinical signs/symptoms. A targeted symptom directed examination is required prior to DCDT2980S or DCDS4501A dosing on Day 2 of each cycle if given on separate days from rituximab only if clinically indicated, e.g. to follow -up on signs or symptoms observed from the examinations performed on Day 1.

[h] Patients will be followed for safety for 30 days after the last infusions of DCDT2980S, DCDS4501A, or rituximab. Such follow-up will require an assessment (per verbal report, at minimum) of any AEs and/or SAEs through 30 days after the last dose of study drug or until the patient receives another anti-cancer therapy including crossover treatment, whichever occurs first. Patients who discontinue study treatment for reasons other than progressive disease will continue to be followed for response for up to 1 year after the last infusions of DCDT2980S or DCDS4501A and rituximab, or until disease progression or initiation of another anti-lymphoma/leukemia therapy, whichever occurs first. Refer to Appendix A-3 for schedule of assessments during the post-treatment period.

Appendix A-2 (cont.)
Study Flowchart: Crossover Treatment *(Patients Randomized to Arms A or B Only)*

[i] Tumor assessments should be performed at screening and every 3 months while receiving study treatment. Tumor assessments should also be performed 28–56 days after the last study drug infusion as part of the crossover treatment completion/early termination visit. Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C).

[j] Administer DCDT2980S or DCDS4501A over 90 minutes for Cycle 1 and over 30 minutes in subsequent cycles if there are no infusion-related adverse events. For Cycle 1b and Cycle 2b, DCDT2980S or DCDS4501A should be administered on the day after rituximab is administered, e.g., Day 2 if rituximab is given on Day 1, or Day 3 if rituximab is given as a split dose on Days 1 and 2. In the absence of any infusion-related adverse events, rituximab followed by DCDT2980S or DCDS4501A may be administered on the same day in subsequent cycles starting with Cycle 3b. Study drug infusions should occur on the scheduled 21-day (or 28-day) cycle, but may be given up to ± 2 days from the date scheduled (i.e., with a minimum of 19 days between doses) if required for logistical/scheduling reasons. Doses may also be delayed up to 2 weeks for recovery from reversible toxicity.

[k] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[l] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), and uric acid.

[m] A serum pregnancy test should be performed for women of childbearing potential performed within 14 days prior to receiving first study treatment. In addition, a serum or urine pregnancy test must also be performed within 10 days prior to Day 1 of Cycles 3, 6, 9, 12, and 15, and at the crossover treatment completion/early termination visit. If any urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

[n] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[o] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[p] Optional tumor biopsy of a safely accessible site of disease, defined as requiring only local anesthesia and in general excluding brain, lungs or any internal organs that may subject patients to significant risk. Tumor samples will be used for research purposes.

Appendix A-3
Study Flowchart: Post-Treatment Follow-Up

Assessments/Procedures	Post-treatment Follow-up				
Months after treatment completion visit	2 Months	4 Months	6 Months	9 Months	12 Months
Targeted physical examination [a]	x	x	x	x	x
Vital signs (blood pressure, pulse rate, and body temperature)	x	x	x	x	x
ECOG Performance Status	x	x	x	x	x
B symptoms [b]	x	x	x	x	x
Tumor assessments [c]	x	x	x	x	x
Total IgA, IgG, IgM	x	x	x	x	x
Hematology [d]	x	x	x	x	x
Serum chemistry [e]	x	x	x	x	x
Bone marrow [f]	Perform to confirm CR if positive for disease at screening or if clinically indicated				
Central Lab Assessments					
Leukocyte immunophenotyping (FACS) [g]	x	x	x	x	x
Pharmacokinetic sampling [h]	x	x	x		
Serum sample for anti-DCDT2980S / anti-DCDS4501A ATA assay [h]	x	x	x		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATA = anti-therapeutic antibody; CR = completed response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescent-activated cell sorter; Ig = immunoglobulin; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PET = positron emission tomography.

NOTE: Post-treatment assessments apply to patients who discontinue from study treatment (initial or crossover treatment) for reasons other than disease progression. The schedule corresponds to visits timed from treatment completion/early termination visit or crossover treatment completion/early termination visit until the time of disease progression, start of new anti-cancer therapy, or withdrawal from study participation. Two-month and 4-month follow-up visits should occur within ±7 days from the scheduled date, while subsequent visits should occur within ±14 days from the scheduled date.

[a] Targeted physical examinations should be limited to systems of clinical relevance (see Section 4.5.1.3) and those systems associated with clinical signs/symptoms.

[b] Defined as unexplained weight loss > 10% over previous 6 months, fever (> 38°C/100.4°F), and/or drenching night sweats.

[c] Response should be assessed based on physical examination and imaged-based evaluation, using standard NHL criteria (Appendix C).

[d] Includes complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, absolute neutrophil count, and percent or absolute differential counts [e.g., segmented neutrophils bands, lymphocytes, eosinophils, monocytes, basophils, and other cells]).

[e] Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (or local equivalent), creatinine, calcium, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), and uric acid.

Appendix A-3 (cont.)
Study Flowchart: Post-Treatment Follow-Up

[f] Bone marrow biopsy for morphology (aspirate for morphology and/or flow studies are optional) should be repeated only to confirm a CR where presence of tumor was documented at the screening bone marrow examination.

[g] A 5-mL whole-blood sample will be taken for the assessment of B cells, T cells, and NK cells.

[h] Refer to Appendices B-1 or B-2.

Appendix B–1
Serum and Plasma Pharmacokinetic Schedule for DCDT2980S/DCDS4501A and Rituximab, and ATA Schedule for DCDT2980S/DCDS4501A (For Patients Receiving Rituximab on Day 1 and DCDT2980S/DCDS4501A on Day 2 of Every Cycle)

Study Visit	Sample Timepoint(s) [a]	Samples [e]
Cycle 1, Day 1	Pre-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycle 1, Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • DCDT2980S/DCDS4501A PK [b]
	30 minutes (±15 minutes) post- DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 1, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 1, Day 15 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycles 2–3, Day 1	Pre-rituximab dose	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycles 2–3, Day 2	Pre- DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 3, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 3, Day 15 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycles 4, and every 4th cycle thereafter), Day 1	Pre-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
Cycles 4, and every 4th cycle thereafter), Day 2	Pre-DCDT2980S/DCDS4501A infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (± 15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK

Appendix B-1 (cont.)
Serum and Plasma Pharmacokinetic Schedule for DCDT2980S/DCDS4501A and Rituximab, and ATA Schedule for DCDT2980S/DCDS4501A (For Patients Receiving Rituximab on Day 1 and DCDT2980S/DCDS4501A on Day 2 of Every Cycle)

Study Visit	Sample Timepoint(s) [a]	Samples [e]
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK
Post-treatment Follow-Up Visits [d]	2, 4, and 6 months after treatment completion visit	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

NOTE: "Pre-infusion" means prior to the start of infusion; "Post-infusion" means after the infusion is completed.

[a] A 3-mL whole-blood sample will be taken for each of the following at each specified timepoint: anti-DCDT2980S or anti-DCDS4501A antibody; rituximab PK; and/or DCDT2980S/DCDS4501A PK. If rituximab dosing is split over two days, then PK will be obtained prior to the rituximab dose on the first day and 30 minutes (±15 minutes) post-rituximab infusion on the second day.

[b] DCDT2980S / DCDS4501A PK including serum PK samples for total DCDT2980S and DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

[c] Cycles 2 and 4 only for anti-DCDT2980S or anti-DCDS4501A antibody.

[d] Post-treatment follow-up PK and ATA assessments only apply to patients who did not receive crossover treatment.

[e] PK sampling will not be obtained from patients who cross-over to another treatment arm.

Appendix B–2
Serum and Plasma Pharmacokinetic Schedule for Rituximab and DCDT2980S/DCDS4501A, and ATA Schedule for DCDT2980S/DCDS4501A for Patients Receiving Rituximab and DCDT29808S/DCDS4501A on Day 1 of Every Cycle Beginning Cycle 3

Study Visit	Sample Timepoint(s) [a]	Samples [e]
For Cycle 1 and Cycle 2 PK assessments, refer to Appendix B-1		
Cycle 3, Day 1	Pre-rituximab infusion	• Rituximab PK • DCDT2980S/DCDS4501A PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Cycle 3, Day 8 (±1 day)		• Rituximab PK • DCDT2980S/DCDS4501A PK
Cycle 3, Day 15 (±1 day)		• Rituximab • DCDT2980S/DCDS4501A PK
Cycles 4, and every 4th cycle thereafter), Day 1	Pre-rituximab infusion	• Rituximab PK • Anti-DCDT2980S/Anti-DCDS4501A antibody [c] • DCDT2980S/DCDS4501A PK
	30 minutes (±15 minutes) post-rituximab infusion	• Rituximab PK
	30 minutes (±15 minutes) post-DCDT2980S/DCDS4501A infusion	• DCDT2980S/DCDS4501A PK
Treatment Completion/ Early Termination Visit	Approximately 15–30 days after last infusion	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK
Post-treatment Follow-Up Visits [d]	2, 4, and 6 months after treatment completion visit	• Anti-DCDT2980S/Anti-DCDS4501A antibody • Rituximab PK • DCDT2980S/DCDS4501A PK

Appendix B–2 (cont.)
Serum and Plasma Pharmacokinetic Schedule for Rituximab and DCDT2980S/DCDS4501A, and ATA Schedule for DCDT2980S/DCDS4501A (For Patients Receiving Rituximab and DCDT29808S/DCDS4501A on Day 1 of Every Cycle Beginning Cycle 3)

ATA = Anti-therapeutic antibody; MMAE = monomethyl auristatin E; PK = pharmacokinetic.

NOTE: "Pre-infusion" means prior to the start of infusion; "Post-infusion" means after the infusion is completed.

[a] A 3-mL whole-blood sample will be taken for each of the following at each specified timepoint: anti-DCDT2980S or anti-DCDS4501A antibody, rituximab PK, and/or DCDT2980S/DCDS4501A PK. If rituximab dosing is split over two days, then PK will be obtained prior to the rituximab dose on the first day and 30 minutes (±15 minutes) post-rituximab infusion on the second day.

[b] DCDT2980S/DCDS4501A PK including serum PK samples for total DCDT2980S and DCDS4501A antibody and plasma PK samples for antibody-conjugated MMAE and free MMAE.

[c] Cycles 4 only for anti-DCDT2980S or anti-DCDS4501A antibody.

[d] Post-treatment follow-up PK and ATA assessments only apply to patients who did not receive crossover treatment.

[e] PK sampling will not be obtained from patients who cross-over to another treatment arm.

Appendix C
Modified Response and Progression Criteria for NHL

Adapted from: Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol 2007;25:579–86.

Selection of Indicator (Target) Lesions

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions

  Abnormal lymph nodes are those that are either

  >15 mm in the greatest transverse diameter (GTD) regardless of the short axis diameter, or

  > 10 mm in short axis diameter regardless of long axis

- If possible, they should be from disparate regions of the body
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

PET Scans--Definition of a Positive PET scan

Visual assessment currently is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary. In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff. Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen uptake, and diffusely increased bone marrow uptake within weeks after treatment.

Complete Remission (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy.

   Typically FDG-avid lymphoma: in patients with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, the designation of CR requires all nodal indicator lesions to regress to the size of normal lymph nodes. Lymph nodes that were > 15 mm in GTD regardless of the short axis diameter at the screening tumor assessment must regress to ≤ 15 mm in GTD regardless of the short axis diameter. Lymph nodes that were 11 to 15 mm in GTD and > 10 mm in the short axis diameter at the screening tumor assessment must regress to ≤ 10 mm in the short axis diameter.

2. The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

3. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (> 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial Remission (PR)

1. ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; (b) if possible they should be from disparate regions of the body; (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
6. No new sites of disease should be observed (e.g., nodes $>$ 1.5 cm in any axis).
7. *Typically FDG-avid lymphoma*: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. *Variably FDG-avid lymphomas/FDG-avidity unknown*: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.
9. In patients with follicular lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease (SD)

1. Failing to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease (see below).
2. *Typically FDG-avid lymphomas*: the PET should be positive at prior sites of disease with no new areas of involvement on the post- treatment CT or PET.
3. *Variably FDG-avid lymphomas/FDG-avidity unknown*: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (RD; after CR) or Progressive Disease (PD; for Patients with PR or SD)

1. Lymph nodes should be considered abnormal if the long axis is $>$ 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1–1.5 cm, it should only be considered abnormal if its short axis is $>$ 1.0. Lymph nodes ≤ 1.0 cm by ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.
2. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities.

3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq$ 50% and to a size of 1.5 $\times$ 1.5 cm or more than 1.5 cm in the long axis.
4. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
5. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 15 mm in its long axis by CT).
6. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease.

Appendix D
Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Appropriate monitors (electrocardiogram, blood pressure, pulse oximetry
- Oxygen
- Tourniquet
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines.
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional assistance!
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible.
- Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix E
M. D. Anderson Symptom Inventory (MDASI)

M.D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24*** hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (symptom is as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1. Your **pain** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
2. Your **fatigue (tiredness)** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
3. Your **nausea** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
4. Your **disturbed sleep** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
5. Your feelings of being **distressed (upset)** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
6. Your **shortness of breath** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
7. Your problems **remembering things** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
8. Your problems with **lack of appetite** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
9. Your feeling **drowsy (sleepy)** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
10. Your having a **dry mouth** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
11. Your feeling **sad** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
12. Your **vomiting** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
13. Your **numbness or tingling** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
14. Your **constipation** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
15. Your **mouth/throat sores** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
16. Your **diarrhea** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯
17. Your problems with **weakness in the arms or legs** at its WORST?	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯	▯

Appendix E (cont.)
M. D. Anderson Symptom Inventory (MDASI)

Part II. How have your symptoms interfered with your life?
Symptoms frequently interfere with how you feel and function. How much have your symptoms interfered with the following items **in the last 24** hours:

	Did Not Interfere										**Interfered Completely**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
18. General activity?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
19. Mood?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
20. Work (including work around the house)?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
21. Relations with other people?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
22. Walking?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
23. Enjoyment of life?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Appendix F
Recommendations for the Use of White Blood Cell Growth Factors

Primary Prophylactic G-CSF Administration (First and Subsequent-Cycle Use)

Primary prophylaxis with G-CSF is recommended if any of the following clinical factors are present:

- Age >65 years
- Poor performance status
- Previous history of febrile neutropenia
- Open wounds or active infections
- More advanced cancer
- Extensive prior treatment, including large radiation therapy ports
- Cytopenias due to bone marrow involvement by tumor
- Other serious comorbidities

Secondary Prophylactic G-CSF Administration

Prophylactic G-CSF administration is recommended for patients who fulfill each of the following circumstances:

- Experienced a neutropenic complication from a prior cycle of study treatment
- Primary prophylactic G-CSF was not received; and
- The intent is to avoid dose reduction of the antibody–drug conjugate (ADC), where the effect of the reduced dose on disease-free, overall survival or treatment outcome is not known

Therapeutic Use of G-CSF

G-CSF administration should be considered for the following patients:

- Patients with febrile neutropenia who are at high risk for infection-associated complications; or
- Patients who have prognostic factors that are predictive of poor clinical outcome, e.g., prolonged (>10 days) and profound (<100/μL) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of fever development

Source: Smith TJ et al. 2006 Update of Recommendations for the use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. JCO 24:3187-3205. 2006.