ML41185

PROTOCOL

TITLE:	**A Phase II Study Evaluating Safety and Efficacy of Polatuzumab Vedotin in Combination with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone in Patients with Previously Untreated Double and Triple Hit Lymphoma, Double Expressor Lymphoma, and High-Grade B Cell Lymphoma**
PROTOCOL NUMBER:	2019-135
VERSION NUMBER:	11
IND NUMBER:	147622
TEST PRODUCTS:	Polatuzumab vedotin
Funding and Drug Supply:	Genentech

PRINCIPAL INVESTIGATOR:

Dipenkumar Modi, M.D.
Karmanos Cancer Institute
4100 John R, Detroit, MI 48201
Modid@karmanos.org
313-576-8739

CO-INVESTIGATORS KCI:	Abhinav Deol, M.D. Andrew Kin, M.D. Ali Gabali, M.D Jay Yang, M.D Melissa Runge-Morris, M.D. Suresh Balasubramanian, M.D. Jeffrey Zonder, M.D. Vijendra Singh, M.D. Craig Cole, M.D. Indryas Woldie, M.D. Jose Larios, M.D.
PARTICIPATING SITES:	TBD

LEAD STUDY COORDINATOR:
Nathan DeLuca, BS, CCRC
Ph: 313-576-9689
delucan@karmanos.org

LEAD REGULATORY COORDINATOR:
Kathy Reichel, BS, CCRP
Ph: 313-576-9374
reichelk@karmanos.org

STATISTICIAN:
Seongho Kim, Ph.D.
Ph: 313-576-8653
kimse@karmanos.org

SPONSOR:
Karmanos Cancer Institute
4100 John R
Detroit, MI 48201
www.karmanos.org
1-800-KARMANOS

Signature Page

Protocol Number: 2019-135

Protocol Title: A Phase II Study Evaluating Safety and Efficacy of Polatuzumab Vedotin in Combination with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone in Patients with Previously Untreated Double and Triple Hit Lymphoma, Double Expressor Lymphoma, and High-Grade B Cell Lymphoma

Approved By:

Dipenkumar Modi, MD

Principal Investigator

Date: February 4, 2025

Protocol Acceptance Page

Protocol Number: 2019-135

Protocol Title: A Phase II Study Evaluating Safety and Efficacy of Polatuzumab Vedotin in Combination with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone in Patients with Previously Untreated Double and Triple Hit Lymphoma, Double Expressor Lymphoma, and High-Grade B Cell Lymphoma

By signing this protocol acceptance page, I confirm I have read, understood, and agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator Name (Printed)

_____

Principal Investigator Signature Date

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

The study protocol and any amendments are to be reviewed by an Institutional Review Board (IRB) before implementation.

Confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent.

TABLE OF CONTENTS

- **TABLE OF CONTENTS**

LIST OF TABLES

LIST OF FIGURES

PROTOCOL SYNOPSIS

TITLE: **A Phase II Study Evaluating Safety and Efficacy of Polatuzumab Vedotin in Combination with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone in Patients with Previously Untreated Double and Triple Hit Lymphoma, Double Expressor Lymphoma, and High-Grade B Cell Lymphoma**

Objectives

1.1 PRIMARY OBJECTIVE

To determine the rate of complete remission (CR) with polatuzumab vedotin (PoV) plus R-CHP in patients with newly diagnosed previously untreated double or triple hit lymphoma, double expressor lymphoma (DEL), and high-grade B cell lymphoma (HGBL) as measured by PET-defined CR rate using the Lugano Response Criteria at the time of primary response assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication)

1.2 SECONDARY OBJECTIVES

1.2.1 Safety Objectives

- To evaluate the safety and tolerability of the combination of PoV plus R-CHP as defined by CTCAE 5.0.

1.2.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are:

- To assess the progression free survival (PFS) with PoV plus R-CHP in the above-mentioned patient population
- To assess the overall survival (OS) with PoV plus R-CHP in the above-mentioned patient population
- To assess the overall response rate (ORR: CR plus PR) at the time of Primary Response Assessment, based on Lugano PET-CT criteria, as determined by the investigator
- To assess the duration of response (DOR) to PoV plus R-CHP based on PET-CT, as determined by the investigators in the above-mentioned patient population

1.2.3 Exploratory Objectives

- To explore the relationship between protein expression of CD79b and response to treatment with PoV plus R-CHP
- To explore the relationship between protein expression of MYC and response to treatment with PoV plus R-CHP
- To explore the relationship of CD79b inhibition on MYC protein expression

Study Design

Description of Study

This is a Phase II, multicenter, open label study of polatuzumab vedotin administered by IV infusion in combination with standard doses of rituximab, cyclophosphamide, doxorubicin, prednisone in patients with untreated double or triple hit lymphoma, double expressor lymphoma, and high-grade B cell lymphoma (HGBL).

A total of 49 patients will be enrolled per a Simon's two-stage optimal design. In the first stage, 13 patients will be treated. If there are 2 or fewer complete responses (CR) in these 13 patients, the study accrual will be suspended. If there are 3 or more complete response, 33 additional patients will be treated for a total of 46. Estimated drop-out rate (including nonevaluable patients) will be 5% and the calculated sample size will be a total of 49.

Number of Patients: 49

1.2.4 Target

Population

Inclusion Criteria

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

- Signed informed consent form (ICF)
- Age ≥ 18 years
- Previously untreated patients (except for one prior cycle of CHOP+R) with DLBCL as determined by local pathology with histology below:
    - Double hit lymphoma (DHL) or triple hit lymphoma (THL) confirmed by FISH testing by local pathology (defined as high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements).
    - Double expressor lymphoma (DEL) defined as overexpression of MYC (≥40%) and BCL2 (>50%) identified by immunohistochemistry (IHC).
    - High grade B-cell lymphoma (HGBL), NOS subtype.
- **NOTE:** *Patients who received anti-lymphoma treatment for prior indolent lymphoma are eligible to participate.* Availability of archival formalin-fixed paraffin-embedded (FFPE) tissue blocks or 15 unstained slides serial sections (3−5 µm in thickness) must be confirmed prior to study enrollment. The pathology report must be available for review and a tissue block sent for retrospective central

confirmation of diagnosis. See case selection. In materials and methods provided in Section 4.4.7.2.

If central confirmation is unable to be performed on submitted material, stained slides used for diagnosis and/or additional tumor tissue specimens may also be requested.

For clarification: Only availability of tumor sample must be verified prior to C1D1 however treatment can commence prior to completion of central review. The adequacy of the tissue will be confirmed if possible (i.e. if it will not delay treatment), however, treatment can commence prior to completion of central review.

- ECOG Performance Status of 0, 1, or 2
- Life expectancy of at least 24 weeks
- At least one bi-dimensionally measurable lesion > 1.5 cm in its longest dimension as measured by CT or MRI
- Ability and willingness to comply with the study protocol procedures
- Left ventricular ejection fraction (LVEF) ≥ 45% on cardiac multiple-gated acquisition (MUGA) scan or cardiac echocardiogram (ECHO)
- Adequate hematologic function (unless due to underlying disease, as established by extensive bone marrow involvement or due to hypersplenism secondary to the involvement of the spleen by DLBCL per the investigator), defined as follows:
    - Hemoglobin ≥ 8.0 g/dL without packed RBC transfusion during 14 days before first treatment
    - ANC ≥ 1,000/μL
    - Platelet count ≥ 75,000/μL
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 12 months after the last dose of study treatment.
    - A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
    - Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    - Women must refrain from donating eggs during the same period.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or

post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- For women of childbearing potential, a negative serum pregnancy test result within 7 days prior to commencement of dosing. Women who are considered not to be of childbearing potential are not required to have a pregnancy test.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:
    - With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 5 months after the last dose of polatuzumab vedotin, 3 months after the last dose of rituximab*, and for at least 6 months after the last dose of cyclophosphamide* to avoid exposing the embryo for the duration of the pregnancy. Men must refrain from donating sperm during this same period.

  Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Male patients considering preservation of fertility should bank sperm before study treatment

Exclusion Criteria

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

- Diffuse large B-cell lymphoma, NOS subtype
- Contraindication to any of the individual components of R-CHOP or any component of PoV, including prior receipt of anthracyclines or history of severe allergic or anaphylactic reactions to humanized or murine MAbs (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Contraindication to rituximab or prior administration of an anti CD 20 antibody
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating DLBCL prior to Cycle 1 Day 1 with the following exceptions:
    - One prior treatment cycle of CHOP+R is allowed. Patients who received one prior R-CHOP will still receive 6 cycles of R-CHP plus Polatuzumab Vedotin per protocol treatment.
    - Glucocorticoid treatment required for lymphoma symptom control prior to the start of study treatment, prednisone 100 mg or equivalent can be given for a maximum of 13 days as a prephase treatment, with all tumor assessments completed prior to starting prednisone
    - One dose of prophylactic intrathecal (IT) chemotherapy with methotrexate
- Grade 3b follicular lymphoma without concurrent DLBCL (evidence of prior grade 3b FL and currently with DLBCL are eligible to participate)
- Primary mediastinal (thymic) large B-cell lymphoma

- Burkitt lymphoma
- Primary or secondary CNS lymphoma (primary or secondary involvement), primary effusion DLBCL, and primary cutaneous DLBCL
- Current Grade 2 peripheral neuropathy per CTCAE 5.0
- History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions include*, but are not limited to*:

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin*,* in situ carcinoma of the cervix *or ductal carcinoma in situ of the breast* at any time prior to the study are eligible.

  Patients with prior indolent lymphoma are eligible.

  A patient with any other malignancy that has been treated with surgery alone with curative intent and the malignancy has been in remission without treatment for ≥ 3 years prior to enrollment is eligible.

  Patients with low-grade, early-stage prostate cancer with no requirement for therapy at any time prior to study are eligible.

  Additional malignant conditions may be approved pending a written approval by the sponsor/medical monitor.
- 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)
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block.
- No evidence of systemic bacterial, viral, or fungal infection at the time of C1D1 Patients with clinical suspicion active or latent tuberculosis (to be confirmed by a positive interferon gamma release assay)
- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HbsAg])

  Patients with occult or prior HBV infection (defined as negative HbsAg and positive hepatitis B core antibody [HbcAb]) may be included if HBV DNA PCR is undetectable, provided that they are willing to undergo DNA testing on Day 1 of every cycle and every 3 months for at least 12 months after the last cycle of study treatment. Patients who have protective titers of hepatitis B surface antibody (HbsAb) after vaccination or prior but cured hepatitis B are eligible.
- Known history of HIV seropositive status

  For patients with unknown HIV status, HIV testing will be performed at Screening
- Vaccination with a live vaccine within 28 days prior to treatment

- Recent major surgery (within 6 weeks before the start of Cycle 1 Day 1) other than for diagnosis
- Women who are pregnant or lactating or who intend to become pregnant within a year of the last dose of study treatment
- Patients with a history of progressive multifocal leukoencephalopathy
- Any of the following abnormal laboratory values, unless abnormal laboratory values are due to underlying lymphoma per the investigator:

  – Creatinine $> 1.5 \times$ ULN or a measured creatinine clearance < 40 mL/min

  – AST or ALT $> 2.5 \times$ ULN

  – Total bilirubin $\geq 1.5 \times$ ULN

    Patients with documented Gilbert disease may be enrolled if total bilirubin is $\leq 3 \times$ ULN.

  – INR or PT $> 1.5 \times$ ULN in the absence of therapeutic anticoagulation

  – PTT or aPTT $> 1.5 \times$ ULN in the absence of a lupus anticoagulant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- The use of Evusheld or other post-exposure anti-viral medications against COVID19 does not affect study eligibility.

End of Study

The end of the study is defined as the time point at which all patients enrolled in the study have completed 5 years of follow-up from the time of the treatment-completion visit or have discontinued the study.

Length of Study: 5 years post last dose of Polatuzumab vedotin and R-CHP

Study Treatment: Polatuzumab Vedotin, Rituximab, CHP

Patients will receive prednisone 100 mg on Day 1 of Cycle 1

Rituximab (or biosimilar) 375 mg/m^2 intravenously on Day 1 of Cycle 1 and on Day 1 of each subsequent cycle for up to six cycles.

Following rituximab infusion, polatuzumab vedotin 1.8 mg/kg will be administered on Day 1 of each cycle

The patient weight obtained during screening (Day -28 to Day -1) should be used for dose determination for all treatment cycles; if the patient's weight within 96 hours prior to Day 1 of a given treatment

cycle > 10% from the weight obtained during screening, the new weight should be used to calculate the dose. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments. All subsequent doses should be modified accordingly. Dose recalculation for polatuzumab vedotin for weight changes <10% are allowed at investigator discretion.

Cyclophosphamide 750 mg/m2 administered IV on Day 1 of each cycle, Doxorubicin 50 mg/m2 administered IV on Day 1 of each cycle for a total of 6 cycles.

Prednisone 100mg daily days 2 through 5 of each cycle

Intrathecal methotrexate 12 mg as CNS prophylaxis on day 1, 2 or 3 of each cycle of therapy Colony/growth factor support on day 3 of each cycle: Neulasta/Udenyca 6mg or Neupogen 300- 400mcg daily for 5-10 days

*Patients who received one prior R-CHOP chemotherapy will still receive 6 cycles of R-CHP plus Polatuzumab vedotin.

Statistical Methods

Determination of Sample Size

The sample size is justified using Simon's two-stage optimal design. The null hypothesis that the true CR rate is 20%) will be tested against the alternative CR rate of 35%. In the first stage, 13 patients will be accrued. If there are 2 or fewer complete responses in these 13 patients, the study will be stopped. Otherwise, 33 additional patients will be accrued for a total of 46. The null hypothesis will be rejected if 13 or more complete responses are observed in 46 patients. This design yields a 1-sided type I error rate of 10% and power of 80% when the true response rate is 35%. Considering the drop-out rate (including nonevaluable patients) of 5%, the required sample size would be 49 patients.

Primary Efficacy Endpoint

Complete remission (CR) rate as measured by PET-CT using the Lugano Response Criteria.

Secondary Efficacy Endpoints

- Progression free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR)
- Duration of response (DOR)

Safety Analyses

Data from all patients who receive at least one study drug will be included in the safety analysis. Safety will be assessed through summaries of adverse events, summaries of changes from screening assessments in laboratory test results, ECGs, and changes in vital signs. All adverse events occurring on or after first study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTC Adverse Event v5.0 toxicity grade. All serious adverse events will be listed separately and summarized. Deaths reported during the study treatment period and those reported

during follow-up after treatment discontinuation will be listed. Relevant laboratory and vital sign (temperature, heart rate, respiratory rate, , and blood pressure) data will be displayed by time, with NCI CTCAE v5.0 Grade 3 and 4 values identified where appropriate.

Exploratory Analyses

Exploratory analyses of biomarkers related to tumor biology and the mechanisms of action of polatuzumab vedotin and rituximab will be conducted. Specifically, the association between candidate biomarkers and PET-CT CR rate and ORR and potentially other measures of efficacy and safety, independent of treatment, will be explored to assess potential prognostic value. In addition, the potential effect modification of treatment effect on PET-CT CR rate and ORR and potential other measures of efficacy and safety, by biomarker status, will be explored to assess potential predictive value.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADC	antibody drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
AML	acute myeloid leukemia
ASCO	American Society of Clinical Oncology
BOR	best objective response
BSA	body surface area
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CL	Clearance
CR	complete response
Cru	complete response unconfirmed
CT	computed tomography
DEL	Double Expressor Lymphoma
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EC	Ethics Committee
EFS	event-free survival
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
FDG	^{18}F-flurodeoxyglucose
G-CSF	granulocyte colony-stimulating factor

Abbreviation	Definition
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HGBL	High grade B cell Lymphoma
HIPAA	U.S. Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug Application
iNHL	indolent non-Hodgkin's lymphoma
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	Intravenous
LMWH	low molecular-weight heparin
LPLV	Last patient last visit
Mab	monoclonal antibody
MC-VC-PABC	maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl
MMAE	mono-methyl auristatin E
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NALT	new anti-lymphoma treatment
NF	New Formulation
NHL	non-Hodgkin lymphoma
OR	objective response
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission topography
PFS	progression-free survival
PK	Pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome
R	Rituximab

Abbreviation	Definition
R/R	relapsed or refractory
SCT	stem cell transplant
SD	stable disease
TEN	toxic epidermal necrolysis
TLS	tumor lysis syndrome
TMA	tissue microarray
ULN	upper limit of normal

1. BACKGROUND

1.1. BACKGROUND ON DISEASE STATE

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin Lymphoma (NHL) accounting for 32,750 new cases every year, and 25% of all cases of NHL in North America and Europe (Swerdlow et al, 2016). It is aggressive lymphoma with male predominance. The incidence increases with age, with the median age of 64 years at diagnosis.

DLBCL is a clinically and biologically heterogeneous disease. Patients present with lymphadenopathy and B symptoms (fever, night sweats, weight loss, and fatigue). Approximately 60% of patients present with advanced stage (stage III or IV disease) disease with 30% of patients harboring bone marrow involvement.

Double hit lymphoma (DHL) is a particularly virulent subset of DLBCL, representing approximately 14% of the newly diagnosed cases. It is defined by simultaneous translocation of MYC gene on chromosome 8 to 14 and a concomitant BCL2 or BCL6 translocation as determined by FISH analysis. When all three abnormalities exist, the nomenclature Triple hit lymphoma (THL) is utilized. The prognosis is DHL and THL is particularly poor when compared to DLBCL regardless of other prognostic features with median PFS and OS of 10.9 months and 21.9 months, respectively.

MYC is a proto-oncogene that produces the transcription factor C-MYC. MYC, located on the long arm of chromosome 8 (8q24), plays an important role in metabolism, protein synthesis, differentiation, stem cell renewal, stress response, messenger RNA (mRNA) regulation, and micro RNA regulation (Sesques and Johnson et al, Blood 2017). MYC controls cell cycle progression and proliferation in part by affecting the transcription of cyclin-dependent kinases. It is a transcriptional amplifier and increases the transcription of genes. BCL2 is located on the chromosome arm 18q21. The primary function of BCL2 is to promote cell survival by inhibiting apoptosis. BCL6 is a transcription factor that suppresses MYC and BCL2 expression in normal GCB cells.

RCHOP given every 21 days remains the standard of care for patients with DLBCL. This

evidence was based on three randomized prospective studies consisting of approximately 2000 older patients (>65 years of age) with advanced stage DLBCL (Coiffier et al 2002; Coiffier et al 2010; Feugier et al 2005).

However, there are no prospective trials evaluating the efficacy of chemotherapies in DHL or THL. RCHOP has been frequently used based on its promising activity in DLBCL. Unfortunately, patients with DHL have dismal outcomes with standard induction chemoimmunotherapy with RCHOP. In a retrospective study of DLBCL patients treated with R-CHOP demonstrated significantly poor outcomes compared to non double hit DLBCL with 5-year PFS of 18% vs 65%, respectively and 5-year OS of 27% vs. 71%, respectively (Johnson et al 2012). These disappointing figures are mirrored in other studies as well, with most Double and THL patients dying of disease within 2 years of diagnosis. In a retrospective study evaluating different chemotherapy regimens, the CR rate in double hit lymphoma after RCHOP was 20% (Oki et al 2014; Petrich et al 2014).

Due to advanced age at diagnosis, medical comorbidities and treatment related toxicities, more intensive therapies are utilized only in a minority of patients. Thus, identifying novel agents that can be used in combination with RCHOP, with manageable toxicity profile are critical to improving outcomes in DHL/THL.

Double expressor lymphoma (DEL), defined as overexpression of MYC (≥ 40%) and BCL2 (>50%) proteins by immunohistochemistry (IHC), accounts for 30% of all DLBCL cases and experiences lower complete response rate, and shorter progression-free and overall survival (Johnson et al 2012, Green et al 2012, Savage et al 2016). Furthermore, in an analysis of 893 patients with de novo DLBCL treated with R-CHOP, multivariate analysis demonstrated that co-expression of MYC/BCL2 was associated with inferior OS (hazard ratio [HR] 2.52; 95% CI 1.73-3.67) and PFS (HR 2.45; 95% CI 1.71-3.51) (Hu et al 2013).

High-grade B-cell lymphoma not otherwise specified (HGBL, NOS) is a recently introduced diagnostic category for aggressive B-cell lymphomas (Swerdlow et al 2017). It includes tumors with Burkitt-like or blastoid morphology that do not have double-hit cytogenetics and that cannot be classified as other well-defined lymphoma subtypes. HGBL, NOS are rare and heterogeneous. Most have germinal center B-cell phenotype, and up to 45% carry a single-hit MYC rearrangement, but otherwise they have no unifying immunophenotypic or cytogenetic characteristics. Recent analyses utilizing gene expression profiling (GEP) revealed that up to 15% of tumors currently classified as diffuse large B-cell lymphoma display a HGBL-like GEP signature, indicating a potential to significantly expand the HGBL category using more objective molecular criteria. Optimal treatment of HGBL, NOS is poorly defined due to its rarity and inconsistent diagnostic patterns. A minority of patients have early-stage disease which can be managed with standard RCHOP-based approaches with or without radiation. For advanced-stage HGBL, NOS, which often presents with aggressive, disseminated disease, high lactate dehydrogenase, and involvement of extranodal organs (including the central nervous system [CNS]), intensified Burkitt lymphoma-like regimens with CNS

prophylaxis may be appropriate. However, many patients diagnosed at age > 60 years are not eligible for intensive immunochemotherapy.

DH and TH lymphoma, DEL, and HGBL patients represent the greatest unmet clinical need in DLBCL according to a recent clinical trials planning meeting from the National Cancer Institute National Clinical Trials Network. R-CHOP is not sufficient induction therapy for this group of patients, as the majority of patients will experience disease progression after standard treatment (Friedberg et al 2017). Therefore, there is an urgent need for novel therapeutic strategies in this high-risk patient population.

1.2. BACKGROUND ON POLATUZUMAB VEDOTIN

1.2.1. Polatuzumab Vedotin Background and Nonclinical 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 chronic lymphocytic leukemia (CLL) samples tested (Dornan et al. 2009). Antibodies bound to CD79b are rapidly internalized, which makes CD79b ideally suited for targeted delivery of cytotoxic agents (Polson et al. 2007; Polson et al. 2009).

Polatuzumab vedotin (DCDS4501A [liquid formulation] and DCDS4501S [lyophilized formulation]) is an antibody drug conjugate (ADC) that contains a humanized immunoglobulin G1 (IgG1) anti-human CD79b MAb (MCDS4409A) and a potent anti-mitotic agent, mono-methyl auristatin E (MMAE), linked through a protease labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-VC-PABC). MMAE has a mode of action similar to that of vincristine, which is a component of standard chemotherapy (e.g., R-CHOP used for treatment of lymphoma). Following binding at the cell-surface epitope and internalization of the ADC by the targeted cell, MMAE is released following cleavage of the linker by lysosomal enzymes. MMAE then binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth (Doronina et al. 2003). This therapeutic approach takes advantage of the specific targeting capability of the antibody and the cytotoxic activity of MMAE and the increased potency of MMAE compared with vincristine. It is hypothesized that the addition of polatuzumab vedotin to a standard anti-CD20 antibody plus chemotherapy regimen will provide enhanced efficacy and safety to patients with NHL.

Comprehensive pharmacologic, pharmacokinetic (PK), pharmacodynamic, and toxicological studies were conducted to support the entry of polatuzumab vedotin into clinical trials. Because polatuzumab vedotin specifically recognizes CD79b on B cells of humans–but not on those of the cynomolgus monkey, rat, or mouse–a surrogate ADC (DCDS5017A) that binds to cynomolgus monkey CD79b was generated to assess the antigen-dependent activities in cynomolgus monkeys. The structure, binding epitope, and binding affinity of the surrogate ADC are similar to that of polatuzumab vedotin. Polatuzumab vedotin has demonstrated efficacy in nonclinical mouse xenograft models of human CD79b-positive NHL. Additionally, polatuzumab vedotin when combined with

rituximab plus chemotherapy (rituximab in combination with cyclophosphamide, doxorubicin, and prednisone [CHP] or bendamustine) demonstrated better anti-tumor activity compared with polatuzumab vedotin as single agent or compared with a current standard of care regimen (R-CHOP or rituximab plus bendamustine [BR]) in xenograft models of NHL. The pharmacokinetics and safety of polatuzumab vedotin and the surrogate ADC were characterized in repeat-dose toxicity studies in rats and cynomolgus monkeys. Polatuzumab vedotin and the surrogate ADC were well tolerated in both species at the tested doses. The predominant antigen-independent findings associated with polatuzumab vedotin or surrogate ADC exposure were reversible bone marrow toxicity and associated peripheral blood cell effects in both monkeys and rats. The PK profiles of polatuzumab vedotin and the surrogate ADC suggested that the pharmacokinetics of the ADC was driven mainly by the antibody component (similar serum concentration-time profile between ADC and total MAb).

Refer to the Investigator's Brochure for complete details of the biochemical composition and nonclinical studies of polatuzumab vedotin.

1.2.1.1. Polatuzumab Vedotin Clinical Data

The original formulation of polatuzumab vedotin is a liquid formulation and was used in the main study (i.e., Phase Ib, Phase II expansion, and Phase II randomized cohorts) in patients with either R/R FL or R/R DLBCL. The liquid formulation is not stable after dilution into saline-containing IV bags, thus requiring a syringe pump for delivery. Therefore, a lyophilized formulation of polatuzumab vedotin has been developed to improve product stability upon dilution into saline-containing IV bags. An initial 170 mg/vial lyophilized configuration was developed and manufactured for a potentially higher dose configuration, which is no longer planned, and is currently in use in other clinical trials only for dosing up to 1.8 mg/kg. A 140 mg/vial drug product was subsequently developed to support a target dose of 1.8 mg/kg. The 170 mg/vial and the 140 mg/vial drug product differ in only the fill volume and yield the same product concentration and composition when reconstituted as prescribed. The lyophilized formulation of polatuzumab vedotin, referred to as "polatuzumab vedotin (lyophilized)" in this protocol, will be used in combination with R-CHP in a Phase II single arm cohort enrolling patients with newly diagnosed double or triple hit lymphoma subtypes of DLBCL.

Complete and updated details of these data are provided in the Polatuzumab Vedotin Investigator's Brochure.

Clinical data on polatuzumab vedotin in patients with NHL or CLL are available from seven Phase I/Ib studies (DCS4968g, JO29138, GO27834, GO29044, GO29365, GO29834, and BO29561) and one ongoing Phase Ib/II studies (, GO29833) in patients with
B-cell lymphoma:

- DCS4968g evaluating safety and tolerability and anti-tumor activity of polatuzumab vedotin and determining the maximum tolerated dose (MTD)/RP2D as a single agent and in combination with rituximab in R/R (Phase I study)
- JO29138 is evaluating polatuzumab vedotin as a single agent in Japanese patients with R/R B-cell lymphoma.
- GO27834 is evaluating polatuzumab vedotin in combination with either obinutuzumab or rituximab in patients with R/R follicular lymphoma (FL) or DLBCL (Phase II study).
- GO29044 is evaluating polatuzumab vedotin in combination with R-CHP or obinutuzumab plus CHP in patients with newly diagnosed or R/R B-cell lymphoma.
- GO29365 is evaluating polatuzumab vedotin in combination with bendamustine plus rituximab or obinutuzumab in patients with R/R FL or DLBCL.
- GO29833 is evaluating polatuzumab vedotin in combination with venetoclax and either obinutuzumab or rituximab in patients with R/R FL or DLBCL, respectively.
- GO29834 is evaluating polatuzumab vedotin in combination with lenalidomide and either obinutuzumab or rituximab in patients with R/R FL or DLBCL, respectively.
- BO29561 is evaluating polatuzumab vedotin in combination with atezolizumab and either obinutuzumab or rituximab in patients with R/R FL or DLBCL, respectively.
- Phase Ib/II study: Polatuzumab Vedotin in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone (R-CHP) for patients with previously untreated Diffuse Large B-cell Lymphoma

Study DCS4968g (Phase I): Polatuzumab Vedotin Monotherapy and Polatuzumab Vedotin in Combination with Rituximab

A total of 95 patients have been enrolled into the Phase I study (Study DCS4968g), of whom 32 patients with NHL (indolent NHL [iNHL] or DLBCL) were enrolled in single-agent dose escalation, 11 patients were enrolled in an iNHL single-agent expansion cohort, 23 patients were enrolled in the DLBCL single-agent expansion cohort, and 9 patients were enrolled in the Phase Ib polatuzumab vedotin plus rituximab combination treatment cohort. Enrollment of patients with NHL into the study has been completed.

The remaining 20 patients, all with CLL, were enrolled into single-agent dose escalation cohorts. For details regarding the clinical data in patients with CLL, refer to the Polatuzumab Vedotin Investigator's Brochure.

Safety

As of 28 February 2013, preliminary safety data were available for all 95 patients enrolled in the dose-escalation and expansion cohorts.

Dose-Limiting Toxicities in NHL

A dose-limiting toxicity (DLT) of Grade 4 neutropenia occurred in 1 of 10 DLT-evaluable patients in the 2.4-mg/kg single-agent cohort and in

1 of 9 DLT-evaluable patients in the 2.4-mg/kg + rituximab cohort. Doses of polatuzumab vedotin > 2.4 mg/kg as monotherapy or in combination with rituximab were not assessed. Consequently, polatuzumab vedotin at 2.4 mg/kg was determined to be the RP2D as both monotherapy and in combination with rituximab. Due to additional information about the risk/benefit profile of polatuzumab vedotin at the 2.4-mg/kg dose, the Sponsor is no longer pursuing the 2.4-mg/kg dose of polatuzumab vedotin.

Treatment Discontinuations Due to Adverse Events

As of the clinical data cutoff date, study treatment discontinuation because of adverse events not due to the disease under study was reported in 19 of 95 patients (20.0%) and study treatment related adverse event leading to treatment discontinuation in 17 of 95 patients (17.9%).

The treatment-related events included Grade 2 peripheral neuropathy (9 patients), Grade 3 peripheral neuropathy (3 patients), Grade 4 peripheral neuropathy (1 patient), Grade 3 diarrhea (1 patient), and Grade 2 hyperesthesia, Grade 2 asthenia, Grade 3 anemia, and Grade 4 thrombocytopenia (each occurring in 1 patient). Two adverse events resulting in treatment discontinuation were reported as not related to study treatment and not due to the disease under study: Grade 3 worsening hyponatremia (1 patient) and Grade 4 invasive fungal infection (1 patient).

Adverse events resulting in study treatment discontinuation that were considered not related to the disease under study were reported in 6 patients with DLBCL: Grade 2 peripheral neuropathy (4 patients), Grade 3 peripheral neuropathy (1 patient), and Grade 3 diarrhea (1 patient). The only adverse event resulting in treatment discontinuation that was considered not related to the disease under study among the patients with CLL was Grade 4 invasive fungal infection (1 patient). All other events were reported in patients with iNHL, including five events of Grade 2 peripheral neuropathy (4 patients), two events of Grade 3 peripheral neuropathy (2 patients), one event of Grade 3 neutropenia (1 patient), and one Grade 2 mucosal inflammation (1 patient). One patient with iNHL experienced five events that led to study treatment

discontinuation (Grade 2 hyperesthesia, Grade 2 asthenia, Grade 3 anemia, Grade 3 thrombocytopenia, and Grade 4 thrombocytopenia).

Adverse Events with Single-Agent Polatuzumab Vedotin

Adverse events, regardless of relationship to study drug, were reported in all 66 patients (100%) with NHL (iNHL+DLBCL) who were treated with single-agent polatuzumab

vedotin. Treatment-emergent adverse events reported in >20% of patients included neutropenia (44%), diarrhea (38%), pyrexia (32%), nausea (32%), peripheral neuropathy (30%), fatigue (23%), and cough (21%).

Grade ≥3 adverse events, regardless of relationship to study drug, were reported in 48 of 66 patients (72.7%) with NHL (iNHL or DLBCL). Neutropenia was the most common adverse event experienced by more than 35% of the 66 patients with NHL. Thirty-one of 45 patients (68.8%) treated at the RP2D of 2.4 mg/kg experienced a Grade 3–5 adverse event. Grade 3–4 adverse events of neutropenia were experienced by >10% of the patients. Three Grade 5 events were reported: 1 patient died of sepsis, 1 patient died of pulmonary vascular disorder, and 1 patient died from an unknown cause. None of the deaths was assessed by the investigator as related to study treatment.

Adverse Events with Polatuzumab Vedotin Combined with Rituximab

In the Phase Ib cohort of Study DCS4968g, adverse events—regardless of relationship to study drug—were reported in 9 of 9 patients (100%) who received polatuzumab vedotin (2.4 mg/kg) plus rituximab (375 mg/m²). The most common adverse events reported in ≥2 patients were neutropenia, pyrexia, nausea, diarrhea, hyperuricemia, bone pain, fatigue, peripheral neuropathy, decreased appetite, chills, pain in extremity, pruritus, arthralgia, night sweats, hypokalemia, dysgeusia, increased blood creatinine, infusion-related reactions (IRRs), cough, constipation, thrombocytopenia, anemia, hyperglycemia, rash, alopecia, hypomagnesemia, upper abdominal pain, hyperhidrosis, myalgia, peripheral motor neuropathy, febrile neutropenia, hyperbilirubinemia, and tooth fracture.

Grade ≥3 adverse events, regardless of relationship to study drug, were reported in 7 of 9 patients (77.8%) receiving polatuzumab vedotin in combination with rituximab in the Phase Ib cohort of Study DCS4968g. Grade 3–4 neutropenia was reported in 5 patients, Grade 3–4 anemia in 2 patients, Grade 3–4 febrile neutropenia in 2 patients, and Grade 3–4 hyperglycemia in 2 patients. No Grade 5 adverse events were reported.

Serious Adverse Events

From ongoing Phase I Study DCS4968g, a total of 44 serious adverse events were reported among 22 patients in the single-agent NHL (iNHL plus DLBCL) cohorts, 19 serious adverse events were reported in 11 patients in the CLL cohort, and 15 serious adverse events were reported in 4 patients treated with polatuzumab vedotin plus rituximab. Among all patients, the most common serious adverse events (occurring in ≥2% of patients) were: Grade 1–2 pyrexia (6 patients), Grade 3–4 febrile neutropenia (4 patients), Grade 4–5 lung infection (3 patients), Grade 3–4 diarrhea (3 patients), Grade 3–4 hyperglycemia (2 patients), Grade 3–4 hyponatremia (2 patients), Grade 2–3 mental status changes (2 patients), Grade 3–4 peripheral neuropathy (2 patients), Grade 3–4 neutropenia (2 patients), Grade 4–5 pneumonia (2 patients), and acute renal failure (Grade 1 in 1 patient and Grade 4 in 1 patient).

Anti-Tumor Activity

Preliminary anti-tumor activity data for best overall response were available for 88 of 95 patients (92.6%) as of the clinical data cutoff date. Eighty-six of 88 patients (97.7%) had R/R iNHL, DLBCL, or CLL. Most evidence of anti-tumor activity was observed at ADC doses ≥1.8 mg/kg. Among patients with R/R iNHL, 13 of 22 patients (59%) treated with single-agent polatuzumab vedotin and 6 of 8 patients (75%) treated with polatuzumab vedotin plus rituximab had an investigator-assessed objective response (OR). Among patients with R/R DLBCL, 14 of 26 patients (54%) treated with single-agent polatuzumab vedotin and 1 of 1 patient treated with polatuzumab vedotin plus rituximab had investigator-assessed OR. Data regarding duration of response (DOR), PFS, and OS were insufficiently mature for reporting.

Study GO27834 (Phase II): Polatuzumab Vedotin in Combination with Rituximab

Safety

As of the clinical data cutoff (22 February 2013), preliminary clinical safety data were available for all 15 patients enrolled and randomized to the polatuzumab vedotin plus rituximab treatment arm. Treatment discontinuation due to adverse events had not been reported for any patient.

Adverse events, regardless of relationship to study drug, were reported in 15 of 15 patients (100%) who received polatuzumab vedotin (2.4 mg/kg) plus rituximab (375 mg/m²). The most common adverse events (all grades) reported in ≥2 patients were fatigue, nausea, diarrhea, neutropenia, vomiting, dry mouth, asthenia, arthralgia, back pain, and headache.

Grade ≥3 adverse events, regardless of relationship to study drug, were reported in 4 of 15 patients (26.7%) receiving polatuzumab vedotin in combination with rituximab. Grade 3–4 neutropenia was reported in 2 patients, Grade 3 diarrhea was reported in 1 patient, Grade 3 chest pain was reported in 1 patient, Grade 3 decreased neutrophil count was reported in 1 patient, and Grade 3 hypophosphatemia was reported in 1 patient.

A total of two serious adverse events were reported in 2 patients treated with polatuzumab vedotin plus rituximab: Grade 2 pyrexia and Grade 2 chest tightness. Both serious adverse events were reported as not related to study drug treatment.

Anti-Tumor Activity

In this ongoing study, anti-tumor activity data were not sufficiently mature to report as of the clinical data cutoff date, because most patients had not yet undergone on-treatment tumor assessments to evaluate response.

Phase Ib/II study: Polatuzumab Vedotin in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone (R-CHP) for patients with previously untreated Diffuse Large B-cell Lymphoma

Safety

As of data cut off February 5, 2016, clinical safety data are available for all 36 evaluable patients. The most common adverse events in > 20% of patients were fatigue (36%), and diarrhea (30%), nausea (31%), and neutropenia (25%).

Forty-four percent of patients had at least one grade 3/4 adverse events including neutropenia (22%), febrile neutropenia (14%), hypertension (8%), thrombocytopenia (4%), leukopenia (4%), oral fungal infection (4%), dysphagia (4%), vomiting (4%), asthenia (4%), fatigue (4), decreased appetite (4%), hyponatremia (4%), malnutrition (4%), chylothorax (4%), back pain (4%), motor dysfunction (4%), and confusional state (4%).

Serious adverse events were reported in 33% of patients, with 17 different events. These included 4 episodes of febrile neutropenia, 2 of neutropenia, 2 of pneumonia, and 1 each of E. coli UTI, oral fungal infection, hyponatremia, malnutrition, chylothorax, pulmonary embolism, pyrexia, pathologic femur fracture, and worsening of rheumatoid arthritis.

Thirty-three percent of patients experienced peripheral neuropathy (PN). The reported terms included PN, paresthesia, muscular weakness, neuralgia, and motor dysfunction. All neurologic adverse events attributed to PoV were Grade 1 except one PN that was Grade 2 and improved to Grade 1 after PoV dose reduction. There were 2 patients that discontinued study treatment due to adverse events (one with a Grade 2 tremor who is still in CR, and the other with Grade 2 UTI who ultimately progressed) while 5 (14%) had PoV dose reductions (2 PN, 2 neutropenia, 1 weight decrease and asthenia). No Grade 5 adverse events were reported among the expansion cohort.

Anti-tumor activity

At the time of data cutoff (February 5, 2016), response assessments were available in 26 pts. All pts in the escalation phase have completed study treatment and 8 in expansion cohort have completed study treatment. In dose escalation phase of the study, end of treatment PET/CT showed complete remission in 80% of patients and partial remission in 20% of patients, while the end of treatment PET/CT revealed complete remission in 54% of patients, partial remission in 23% of patients and progressive disease in 15% of patients in dose expansion phase of the study.

Given these findings, the dose of PoV was recommended to be 1.8 mg/kg in combination with R-CHP.

1.2.1.2. Pharmacokinetic and Pharmacodynamic Properties of Polatuzumab Vedotin

The PK properties of polatuzumab vedotin conjugate (evaluated as antibody-conjugated MMAE [acMMAE]), total antibody, and unconjugated MMAE after the first dose of polatuzumab vedotin in patients with NHL, either as a single agent or in combination with rituximab, are summarized below.

In patients with NHL, polatuzumab vedotin demonstrated a trend of linear pharmacokinetics for each measurement across the dose range from 0.1 to 2.4 mg/kg. On the basis of the results from DCS4968g, 2.4 mg/kg in patients with NHL, serum concentrations of total antibody and acMMAE reached peak values at the end of infusion. The distribution of total antibody and acMMAE appears to be restricted to the serum compartment, with mean steady-state volume of distribution (V_{ss}) values of approximately 70–87 mL/kg and approximately 93–109 mL/kg for acMMAE and total antibody, respectively. Mean clearance (CL) of acMMAE (approximately 15–21 mL/day/kg) was similar to CL of total antibody (approximately 11–19 mL/day/kg), suggesting that acMMAE CL was largely dominated by its antibody component. Mean terminal half-life for acMMAE was approximately 5.1–6.4 days and total antibody, approximately 8.1 days.

Unconjugated MMAE reached maximal concentrations at 2.01–3.42 days after the first dose, suggesting a delayed formation due to catabolism of the conjugate. There was a trend of increased C_{max} and AUC_{inf} values with conjugate dose increase. At each dose level, C_{max} and AUC_{inf} values for unconjugated MMAE were substantially lower compared with its parent analyte acMMAE, suggesting that the total MMAE level in the systemic circulation after conjugate administration was mainly composed of conjugated MMAE. The $t_{½}$ values ranged from 2.93–5.81 days, which are relatively long for a small molecule and similar to the $t_{½}$ value for conjugate, suggesting that the kinetics of unconjugated MMAE could be dominated by its formation from the conjugate. On the basis of the $t_{½}$ values, a small amount of accumulation was expected upon every 3-week dosing.

The PK profiles and parameters were similar in the absence and presence of rituximab, suggesting that rituximab has little impact on polatuzumab vedotin PK in the R/R NHL patient population. Given the various CYPs involved for metabolism of MMAE and bendamustine, the risks of PK interactions between them is low.

See the Polatuzumab Vedotin Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3. STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

RCHOP is the standard first line treatment for untreated DLBCL. Unfortunately, DHL and THL, DEL, and HGBL, NOS subtypes of DLBCL characterized by aggressive disease, are typically chemo- refractory and are associated with short survival and poor

prognosis independent of the International Prognostic Index. The complete response rate with standard R-CHOP is very poor at 20%, with dismal long term PFS and OS. Therefore, aggressive chemotherapy regimens including R-EPOCH, R-HyperCVAD/MA, and R-CODOX- M/IVAC have been evaluated in retrospective studies; however, these chemotherapy regimens can not be used in a substantial proportion due to age and comorbidities and have not demonstrated better outcomes prospectively in double/triple hit lymphoma, and double expressor lymphoma (Wilson et al 2016) (ASH abstract 469 2016) Therefore, new therapeutic modalities, are indeed needed to improve outcomes in this high-risk population.

Polatuzumab vedotin, an antibody drug conjugate (ADC) that delivers the microtubule inhibitor mono-methyl auristatin E (MMAE)in a targeted fashion to cells expressing CD79b, has been evaluated in previously untreated DLBCL as a replacement strategy for the microtubule inhibitor vincristine. CD79b is a cell surface antigen that is expressed ubiquitously on DLBCL tumor cells, as well as other mature B cells (Olejniczak et al. 2006; Pfeifer et al. 2015). The expression pattern of this surface antigen enables the application of polatuzumab vedotin in all DLBCL subtypes (Pfeifer et al. 2015). The use of a replacement strategy enables continuation of the dosing regimen of R-CHP every 21 days.

Polatuzumab vedotin at doses between 1.8 mg/kg and 2.4 mg/kg has demonstrated promising anti-tumor efficacy in R/R DLBCL as a single agent and in combination with an anti-CD20 monoclonal antibody. However, in this patient population, the higher 2.4 mg/kg dose administered for up to seventeen 21-day cycles resulted in hematologic, infectious, and neurologic toxicity. In the Phase Ib/II study GO29044 evaluating the recommended Phase II dose of polatuzumab vedotin at 1.8 mg/kg every 21 days with RCHP in patients with previously untreated DLBCL, the safety profile was comparable to that seen in the RCHOP arm of the contemporary study BO21005/GOYA (Vitolo et al. 2016). These patients in GO29044 experienced similar rates of Grade 3 and 4 adverse events (57.8% vs. 60.3%), Grade 5 adverse events (2.2% vs. 4.3%), and severe adverse events (37.8% vs. 37.6%) when compared with the R-CHOP arm of BO21005/GOYA. This dosing schedule is consistent with an analysis performed by the FDA in which the recommended Phase II human dose across eight ADC development programs using the same protease-cleavable valine-citrulline-MMAE platform, which is between 1.8 mg/kg and 2.4 mg/kg when the ADC is given every 21 days (Saber and Leighton 2015).

Pharmacokinetic studies did not demonstrate alterations to cyclophosphamide or doxorubicin pharmacokinetics when combined with polatuzumab vedotin, and dose intensity of R-CHP was also maintained with the incorporation of polatuzumab vedotin at 1.8 mg/kg. Efficacy by positron emission tomography (PET), as measured by investigator-assessed response by Cheson 2007 criteria, was promising, with 78% achieving CR and 91% achieving overall response at the end of treatment (10).

Given the promising activity and favorable safety profile of PoV in combination with R-CHP in R/R DLBCL, it may be beneficial to evaluate this regimen in double or triple hit

Lymphoma, double expressor lymphoma, and HGBL, NOS subtype. The objective of the current single arm phase II study is to evaluate the safety and efficacy of PoV plus R-CHP in 49 patients with previously untreated DHL and THL, double expressor lymphoma, and HGBL, NOS subtype.

2. OBJECTIVES

2.1. PRIMARY OBJECTIVE

To determine the rate of complete remission (CR) with polatuzumab vedotin plus R-CHP in patients with newly diagnosed previously untreated double or triple hit lymphoma, double expressor lymphoma, and high-grade B cell lymphoma (HGBL) as measured by PET-defined CR rate using the Lugano Response Criteria at the time of primary response assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication)

2.2. SECONDARY OBJECTIVES

2.2.1. Safety Objectives

- To evaluate the safety and tolerability of the combination of PoV plus R-CHP as defined by CTCAE 5.0.

2.2.2. Secondary Efficacy Objectives

The secondary efficacy objectives for this study are:

- To assess the progression free survival (PFS) with PoV plus R-CHP in the above-mentioned patient population
- To assess the overall survival (OS) with PoV plus R-CHP in the above-mentioned patient population
- To assess the overall response rate (ORR; CR or PR) at the time of Primary Response Assessment, based on Lugano PET-CT criteria, as determined by the investigator
- To assess the duration of response (DOR) to PoV plus R-CHP based on PET-CT, as determined by the investigators in the above-mentioned patient population

2.2.3. Exploratory Objectives

- To explore the relationship between CD79b expression and response to treatment with PoV plus R-CHP
- To explore the relationship between MYC expression and response to treatment with PoV plus R-CHP
- To explore polatuzumab vedotin treatment on Myc protein expression

3. STUDY DESIGN

3.1. DESCRIPTION OF THE STUDY

This is a Phase II, multicenter, open label study of polatuzumab vedotin administered by IV infusion in combination with standard doses of rituximab, cyclophosphamide, doxorubicin, prednisone in patients with untreated double or triple hit lymphoma, double expressor lymphoma (DEL), and high-grade B cell lymphoma (HGBL).

A total of 49 patients will be enrolled per a Simon's two-stage optimal design. In the first stage, 13 patients will be treated. If there are 2 or fewer responses in these 13 patients, the study accrual will be suspended. If there are 3 or more response, 33 additional patients will be treated for a total of 46. The estimated drop-out rate (including nonevaluable patients) is 5% and the calculated sample size includes 49 total patients.

3.1.1. SCREENING

WITHIN 28 DAYS PRIOR TO REGISTRATION FOR PROTOCOL THERAPY:

- Informed consent obtained
- Patient must satisfy all the inclusion criteria and absence of any exclusion criterion.
- Confirmation of diagnosis of DHL or THL by local pathology testing and submission of pathology and FISH reports confirming diagnosis to KCI
- Confirmation of availability of tissue sample
- Physical exam and ECOG PS
- Vital signs: temperature, blood pressure, pulse rate, respiratory rate, weight, height, and body surface area (BSA) (screen only).
- Complete blood count with differential (CBC): to include basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, monocytes, neutrophils, platelet count, red blood cell count, total white cell count.
- Comprehensive metabolic panel (CMP): to include albumin, alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase, bicarbonate, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, uric acid, potassium, sodium, total bilirubin, , total protein, BUN/urea or blood urea nitrogen (depending on local practice).
- B2-microglobulin
- HBA1C
- Coagulation: INR or PT, and PTT or aPTT
- Viral serology:

  Hepatitis B surface antibody (HBsAb), HBsAg, and total HBcAb

  HBV-DNA by PCR if the patient is HBcAb positive

  HCV antibody

HCV RNA by PCR if the patient is HCV antibody positive

- Calculated creatinine clearance using the Cockcroft-Gault formula or by 24-hour urine collection for determination of creatinine clearance.
- [Within 7 days prior to Cycle 1 Day 1 of treatment] Serum pregnancy test for women of childbearing potential
- Electrocardiogram (EKG)
- Echocardiogram or MUGA to evaluate left ventricular ejection function
- Baseline signs and symptoms; concomitant medications.
- PET scan and CT scan with contrast with measurable disease per protocol.

3.1.2. TREATMENT

Patients will receive six cycles of polatuzumab vedotin plus R-CHP at 21-day intervals. The first day of treatment will constitute Study Day 1 and patients will be treated up to a total of six cycles.

*Patients who received one prior R-CHOP chemotherapy will still receive 6 cycles of R-CHP plus Polatuzumab vedotin.

R-CHP + Polatuzumab vedotin: Prednisone 100 mg/day orally given first on days 1 through 5 of every cycle, followed by Rituximab (or biosimilar) 375 mg/m^2 IV infusion, Polatuzumab Vedotin 1.8 mg/kg IV, Cyclophosphamide 750 mg/m^2 IV infusion and Doxorubicin 50 mg/m^2 IV push each given on Day 1 of every 21-day cycle for 6 cycles.

Intrathecal methotrexate 12 mg as CNS prophylaxis on day 1, 2 or 3 of each cycle of therapy

All patients will be evaluated for safety and efficacy according to the schedules of assessments (Appendix 1).

All patients will be assessed for response to treatment by the investigator with the use of standard criteria according to the Lugano Response Criteria (Cheson et al. 2014; see Appendix 2) at screening and at the following time points:

- Interim response assessment (between Cycle 3 Day 15 and Cycle 4 Day 15) by PET/CT
- Primary response assessment: 6–8 weeks after completion of study treatment (i.e., Day 1 of Cycle 6 or after last dose of study medication) by PET/CT

Imaging at interim and primary response assessment must include FDG-PET (18F fluorodeoxyglucose-positron emission tomography) and a diagnostic-quality CT scan with both oral and IV contrast. A combined PET-CT scan is encouraged if feasible.

After discontinuation of therapy, all patients will be followed for 5 years at clinic visits conducted every 3 months for the first 2 years of treatment discontinuation and then every 6 months for the remaining 3 years of follow up until disease progression, death, withdrawal of consent, or initiation of another anti-cancer therapy. CT neck, chest, abdomen and pelvis with contrast will be performed every 6 months for the first year or sooner if clinical suspicion of progression. MRI with contrast can be performed if CT contrast is contraindicated as determined by the treating physician. Tumor assessments should also be performed to confirm disease status including clinical suspicion of relapse or disease progression for documentation. If there is a clinical concern for disease progression, a PET-CT to confirm progression is recommended.

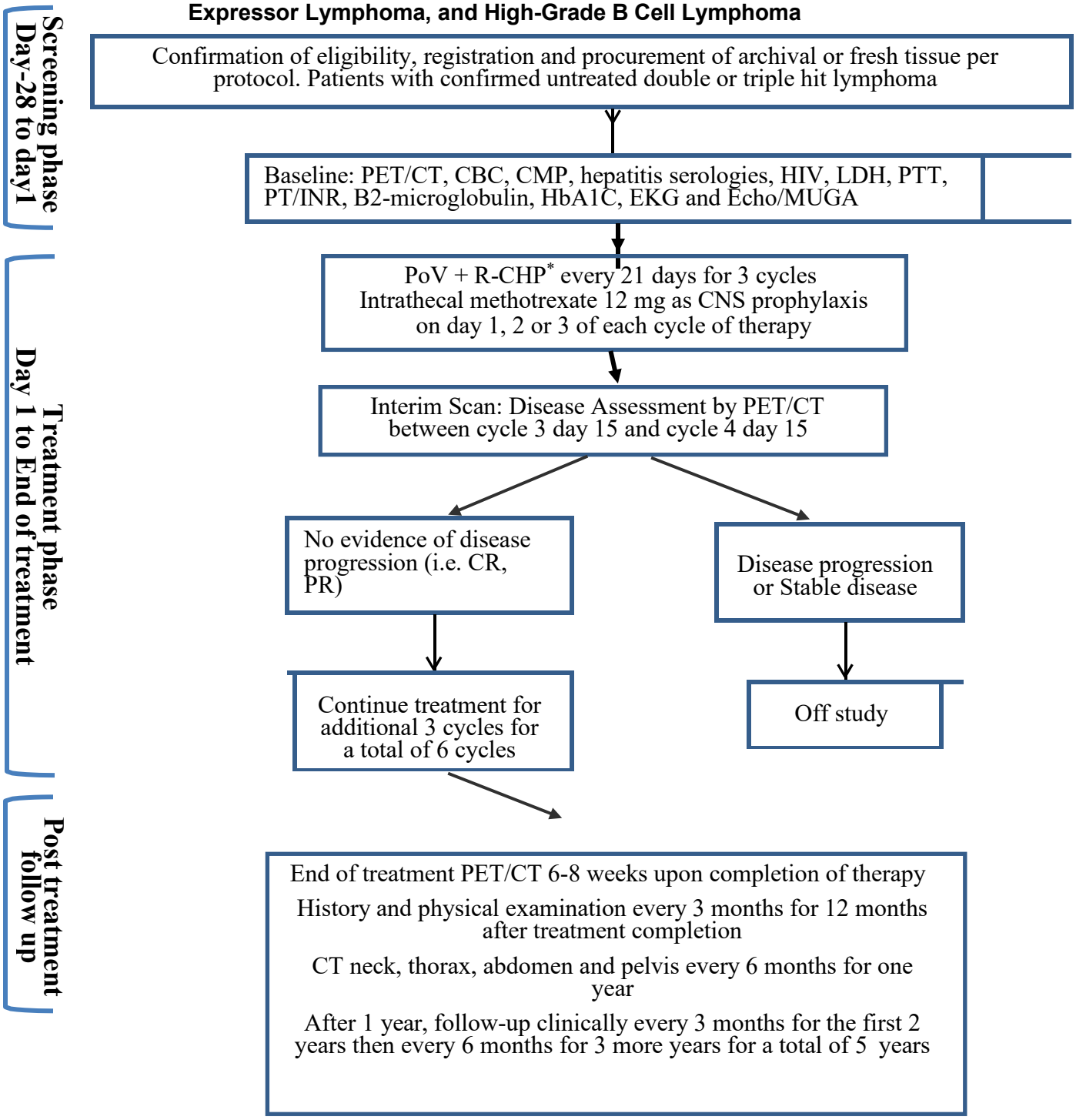
Patients who terminate study treatment prior to 6 cycles of therapy without progressive disease will complete the treatment termination visit and then will be followed for progression, new anti-lymphoma therapy, and OS. Patients who initiate new anti-lymphoma therapy in the absence of progressive disease will be censored at the last

visit. But these patients will be followed for progression, additional new anti-lymphoma therapy, and OS.

Safety will be evaluated by monitoring all adverse events, serious adverse events, and abnormalities identified through physical examinations, vital signs, and laboratory assessments. Such events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). Laboratory safety assessments will include routine monitoring of hematology and blood chemistry, and tests of immunologic parameters.

Figure 1 Study Schema

A Phase II Study Evaluating Safety and Efficacy of Polatuzumab Vedotin in Combination with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone in Patients with Previously Untreated Double and Triple Hit Lymphoma, Double Expressor Lymphoma, and High-Grade B Cell Lymphoma



R-CHP + polatuzumab vedotin:

Day 1: Prednisone 100 mg PO → Rituximab (or biosimilar) 375 mg/m2 IV infusion → PoV 1.8 mg/kg IV → Cyclophosphamide 750 mg/m2 IV infusion → Doxorubicin 50 mg/m2 IV push
Day 2-5: Prednisone 100mg/day PO
Cycle repeated every 21 days

3.2. Safety and Study Oversight

1. Scheduled investigator teleconferences will be held monthly or more frequently depending on the activity of the protocol. These meetings will include the protocol investigators and research staff involved with the conduct of the protocol.

a. During these meetings the investigators will discuss:

1. Safety of protocol participants (adverse events and reporting)

2. Validity and integrity of the data (data completeness on case report forms and complete source documentation)

3. Enrollment rate relative to expectation of target accrual, (eligible and ineligible participants)

4. Retention of participants, adherence to the protocol and protocol deviations

5. Protocol amendments

3.2.1. Internal Monitoring Committee

1. Data and Safety Monitoring Reports (DSMR) will be completed by the Study Coordinator at Karmanos and reflect reported safety data from all sites. The DSMR will be submitted to the Karmanos Data and Safety Monitoring Committee (DMSC) monthly for review. The DSMC will review safety of all study subjects and will recommend continuation or closure of the study. The DSMC will review the safety data monthly and will recommend termination if they judge the rate and severity of AEs to be unacceptable. The DSMC's recommendations will guide study conduct.

2. The Barbara Ann Karmanos Cancer Institute, Data and Safety Monitoring Committee (DSMC) is composed of medical providers, pharmacists and research staff and provides the primary oversight of data and safety monitoring for KCI Investigator-initiated trials.

3.3. END OF STUDY

The end of the study is defined as the time point at which all patients enrolled in the study have completed 60 months (5-years) of follow-up from the time of the treatment-completion visit or have discontinued the study.

3.4. RATIONALE FOR STUDY DESIGN

3.4.1. Rationale for Polatuzumab Vedotin Dose and Schedule

Polatuzumab vedotin dosing for this study was based on the experience from the Phase I Study DCS4968g with single-agent polatuzumab vedotin in relapsed and refractory patients with indolent NHL and DLBCL. Most evidence of anti-tumor activity was observed at doses ≥1.8 mg/kg. To date, over 500 patients have been enrolled in eight trials administering polatuzumab vedotin in B-cell malignancies. At the dose of 1.8 mg/kg every 21 days, polatuzumab vedotin has been well tolerated as monotherapy and in combination with an anti-CD20 monoclonal antibody in patients with R/R B-cell NHL, with expected toxicities including cytopenias and peripheral neuropathy. In patients with previously untreated DLBCL, polatuzumab vedotin at 1.8 mg/kg in combination with R-CHP was administered to 45 patients, and polatuzumab vedotin at 1.8 mg/kg in combination with CHP and another anti-CD20 monoclonal antibody (obinutuzumab) was administered to 17 patients. This constitutes the patient population targeted in this study and provides the rationale for the recommended dose and schedule of PoV, R-CHP in this study.

3.4.2. Rationale for PET-Defined Complete Response

PET scanning has been shown in multiple settings to be a more accurate tool for assessing activity of lymphoma than CT imaging. In aggressive lymphomas, such as DLBCL, PET-defined CR is a better predictor of PFS than response as defined by CT (Barrington et al 2014; Cheson et al 2014).

3.4.3. Rationale for collecting tissue samples for biomarker analysis

Tumor tissue samples will be submitted in all cases prior to starting therapy and at the time of progression/inadequate response if biopsy is obtained. Archival tissue may be submitted. Tissue will be evaluated for CD79 and MYC expression by the sponsor (KCI).

3.5. OUTCOME MEASURES

3.5.1. Safety Outcome Measures

Safety will be a secondary end point in our study and will be assessed by CTCAE 5.0 criteria.

3.5.2. Efficacy Outcome Measures

Response assessment will be determined according to Lugano Response Criteria for Malignant Lymphoma (Lugano Classification; Cheson et al. 2014; see Appendix 2).

- CR at primary response assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) based on PET-CT, as determined by the investigator
- Progression-free survival (PFS) defined as the duration from the start date of the treatment until the date of progression or death from any cause, whichever occurs first
- Overall response (OR) defined as CR or PR at primary response assessment based on PET-CT as determined by the investigator
- Duration of response (DOR) measured from the date of CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is documented among all treated subjects who had a confirmed CR or PR

3.5.3. Exploratory Outcome Measures

The exploratory biomarker outcome measures for this study are as follows:

- Biomarkers will be assessed retrospectively using a tissue block (preferred) or 15 serial freshly cut, unstained slides plus punch biopsy of the tissue block from the time of initial diagnosis and, if possible, at the time of disease progression. Samples should be submitted in all cases prior to initiation of therapy as a baseline sample and subsequently at the time of progression/inadequate response if biopsy is performed.

4. MATERIALS AND METHODS

4.1. PATIENTS

Eligible patients must have previously untreated double or triple hit lymphoma and meet the following inclusion and exclusion criteria.

4.1.1. Inclusion Criteria

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

- Signed informed consent form (ICF)
- Age ≥ 18 years
- Previously untreated patients (except for one prior cycle of CHOP+R) with DLBCL as determined by local pathology. WHO histologies will include:
    - Double hit lymphoma (DHL) or triple hit lymphoma (THL) confirmed by FISH testing by local pathology (defined as high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements)
    - Double expressor lymphoma (DEL) defined as overexpression of MYC (≥ 40%) and BCL2 (> 50%) identified by immunohistochemistry (IHC).
    - High grade B-cell lymphoma (HGBL), NOS subtype.

- **NOTE:** *Patients who received anti-lymphoma treatment for prior indolent lymphoma are eligible to participate*

Availability of archival formalin-fixed paraffin-embedded (FFPE) tissue blocks or 15 unstained slides serial sections (3−5 µm in thickness) must be confirmed prior to study enrollment. The pathology report must be available for review and a tissue block sent for retrospective central confirmation of diagnosis. See case selection. In materials and methods provided in Section 4.4.7.2.

If central confirmation is unable to be performed on submitted material, stained slides used for diagnosis and/or additional tumor tissue specimens may also be requested

For clarification: Only availability of tumor sample must be verified prior to C1D1 however treatment can commence prior to completion of central review. The adequacy of the tissue will be confirmed if possible (ie. if it will not delay treatment).

- ECOG Performance Status of 0, 1, or 2
- Life expectancy of at least 24 weeks
- At least one bi-dimensionally measurable lesion > 1.5 cm in its longest dimension as measured by CT or MRI
- Ability and willingness to comply with the study protocol procedures
- Left ventricular ejection fraction (LVEF) ≥ 45% on cardiac multiple-gated acquisition (MUGA) scan or cardiac echocardiogram (ECHO)
- Adequate hematologic function (unless due to underlying disease, as established by extensive bone marrow involvement or due to hypersplenism secondary to the involvement of the spleen by DLBCL per the investigator), defined as follows:
  - Hemoglobin ≥ 8.0 g/dL without packed RBC transfusion during 14 days before first treatment
  - ANC ≥ 1,000/µL
  - Platelet count ≥ 75,000/µL
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 12 months after the last dose of study treatment.
  - A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
  - Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - Women must refrain from donating eggs during the same period.

- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- For women of childbearing potential, a negative serum pregnancy test result within 7 days prior to commencement of dosing. Women who are considered not to be of childbearing potential are not required to have a pregnancy test.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:
    - With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 5 months after the last dose of polatuzumab vedotin, 3 months after the last dose of rituximab*, and for at least 6 months after the last dose of cyclophosphamide* to avoid exposing the embryo for the duration of the pregnancy. Men must refrain from donating sperm during this same period.
- Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Male patients considering preservation of fertility should bank sperm before study treatment.

4.1.2. Exclusion Criteria

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

- Diffuse large B-cell lymphoma, NOS subtype
- Contraindication to any of the individual components of R-CHOP or any component of PoV, including prior receipt of anthracyclines or history of severe allergic or anaphylactic reactions to humanized or murine MAbs (or recombinant antibody-related fusion proteins) or known sensitivity or allergy to murine products
- Contraindication to rituximab or prior administration of an anti CD 20 antobody.
- Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating DLBCL prior to Cycle 1 Day 1 with the following exceptions:
    - One prior treatment cycle of CHOP+R is allowed. Patients who received one prior R-CHOP will receive 6 cycles of R-CHP plus Polatuzumab Vedotin per protocol treatment.
    - Glucocorticoid treatment required for lymphoma symptom control prior to the start of study treatment, prednisone 100 mg or equivalent can be given for a maximum of 13 days as a prephase treatment, with all tumor assessments completed prior to starting prednisone
    - One dose of prophylactic intrathecal chemotherapy with methotrexate.
- Grade 3b follicular lymphoma without concurrent DLBCL (evidence of prior grade 3b

FL and currently with DLBCL are eligible to participate)

- Primary mediastinal (thymic) large B-cell lymphoma
- Burkitt lymphoma
- Primary or secondary CNS lymphoma (primary or secondary involvement), primary effusion DLBCL, and primary cutaneous DLBCL
- Current Grade 2 peripheral neuropathy per CTCAE 5.0
- History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions include*, but are not limited to*:

  Patients with a history of curatively treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or ductal carcinoma in situ of the breast at any time prior to the study are eligible.

  Patients with prior indolent lymphoma are eligible.

  A patient with any other malignancy that has been treated with surgery alone with curative intent and the malignancy has been in remission without treatment for ≥ 3 years prior to enrollment is eligible.

  Patients with low-grade, early-stage prostate cancer with no requirement for therapy at any time prior to study are eligible.

  Additional malignant conditions may be approved pending a written approval by the sponsor/medical monitor.
- 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)
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block,
- No evidence of systemic bacterial, viral, or fungal infection at the time of C1D1 Patients with clinical suspicion of active or latent tuberculosis (to be confirmed by a positive interferon gamma release assay)
- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg])

  Patients with occult or prior HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) may be included if HBV DNA PCR is undetectable, provided that they are willing to undergo DNA testing on Day 1 of every cycle and monthly for at least 12 months after the last cycle of study treatment. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible.
- Known history of HIV seropositive status

  For patients with unknown HIV status, HIV testing will be performed at

Screening

- Vaccination with a live vaccine within 28 days prior to treatment
- Recent major surgery (within 6 weeks before the start of Cycle 1 Day 1) other than for diagnosis
- Women who are pregnant or lactating or who intend to become pregnant within a year of the last dose of study treatment
- Patients with a history of progressive multifocal leukoencephalopathy
- Any of the following abnormal laboratory values, unless abnormal laboratory values are due to underlying lymphoma per the investigator:
  - Creatinine $>$ 1.5 $\times$ ULN or a measured creatinine clearance $<$ 40 mL/min
  - AST or ALT $>$ 2.5 $\times$ ULN
  - Total bilirubin $\geq$ 1.5 $\times$ ULN

    Patients with documented Gilbert disease may be enrolled if total bilirubin is $\leq$ 3 $\times$ ULN.
  - INR or PT $>$ 1.5 $\times$ ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT $>$ 1.5 $\times$ ULN in the absence of a lupus anticoagulant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- The use of Evusheld or other post-exposure anti-viral medications against COVID19 does not affect study eligibility.

4.1.3. Criteria for Tissue submission

Eligible patients must have available at the study site a representative formalin-fixed, paraffin-embedded tumor specimen that enabled the definitive diagnosis of DLBCL.

- The specimen must contain adequate evaluable tumor cells ($\geq$20% for excisional biopsy and $\geq$50% if sample is a core biopsy) to enable relevant biomarker analysis.
- A tissue block (preferred) or 15 serial, freshly cut, unstained slides plus punch biopsy of the tissue block accompanied by an associated pathology report will be requested. Punch biopsy is required only with the slide submission. Cytological or fine-needle aspiration samples are not acceptable.

If the archival tissue is unavailable or insufficient on the basis of the above criteria, the patient may still be eligible if the patient is willing to provide tissue from a pretreatment core or excisional/incisional biopsy of the tumor. Cytological or fine-needle aspiration samples are not acceptable. Tissue collected on study will not be returned to sites. If needed, additional slides from previously collected samples may be requested.

Cases received from each of the participating institutes should be histological confirmed

according to the 2016 WHO classification of tumors of hematopoietic and lymphoid neoplasm. The evaluation process by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) requires the possession of representative amount of tissues in a paraffin embedded block to be sent to the primary testing institution (Karmanos Cancer Center, Detroit Michigan).

Shipped slides should be placed in proper containers to avoid breakage during shipping. Blocks of paraffin embedded tissue or slides should be sent with a tracking number the address below. In addition, the participation institution should call the laboratory at 313-576-8351 (Julie Boerner) for any sample that they ship and provide tracking number.

Julie Boerner
Karmanos Cancer Institute
4100 John R. St 816 HWCRC
Detroit MI 48201
313-576-8351

4.2. STUDY TREATMENT

4.2.1. Polatuzumab Vedotin plus R-CHP regimen

Polatuzumab vedotin will be administered by IV infusion at 1.8 mg/kg on Day 1 of each 21-day cycle for 6 cycles; Rituximab (or biosimilar), cyclophosphamide, doxorubicin and prednisone (R-CHP) chemoimmunotherapy at standard doses will be administered concurrently every 21 days for each 21-day cycle.

4.2.2. Dosage, and Administration

Schedule for Cycle 1

Cycle 1 Day 1 (± 2 days)

- Prednisone 100 mg oral
- Rituximab 375 mg/m^2 IV infusion
- Polatuzumab Vedotin 1.8 mg/kg IV
- Cyclophosphamide 750 mg/m^2 IV infusion
- Doxorubicin 50 mg/m^2 IV push
- Intrathecal methotrexate 12 mg as CNS prophylaxis (acceptable to administer on day 1, 2 or 3 of each cycle, please see the calendar)

Cycle 1 Day 3

- Colony/growth factor support
    - Neulasta/Udenyca 6mg day 3 or Neupogen 300-480 mcg daily for 5-10 days per institutional guidelines beginning on day 3

Cycle 1 Days 2 through 5

- Prednisone 100 mg oral daily

Schedule for Cycles 2–6

Cycles 2–6 Day 1 (± 2 days)

- Prednisone 100 mg oral
- Rituximab 375 mg/m^2 IV infusion
- Polatuzumab Vedotin 1.8 mg/kg IV
- Cyclophosphamide 750 mg/m^2 IV infusion
- Doxorubicin 50 mg/m^2 IV push
- Intrathecal methotrexate 12 mg as CNS prophylaxis (acceptable to administer on day 1, 2 or 3 of each cycle, please see the calendar)

Cycle 2-6 Days 2 though 5

- Prednisone 100 mg oral daily

Cycle 2-6 Day 3

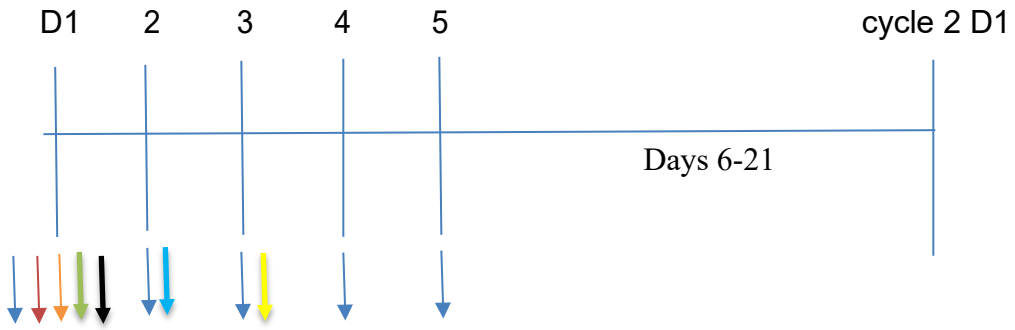
- Colony/growth factor support
    - Neulasta/Udenyca 6mg day 3 or Neupogen 300-480 mcg daily for 5-10 days per institutional guidelines beginning on day 3

A pre-phase treatment of prednisone at a dose of up to 100 mg PO every day for up to 13 days prior to Cycle 1, Day 1 is permitted for tumor related symptom control, at the discretion of the investigator. Vincristine is not permitted at any time on study. The pre-phase treatment is not considered part of study treatment but will be recorded in the electronic Case Report Form (eCRF). Staging study assessments (i.e., bone marrow biopsy, CT/MRI, PET-CT scan, tumor biopsy) must be performed prior to initiation of pre-phase treatment.

The dose of each agent should be calculated on the basis of a patient's body weight at the screening assessment (within 28 days of Cycle 1, Day 1). For changes >10% in body weight from screening for all subsequent doses, the doses of all agents should be modified accordingly to the new weight/body surface area (BSA). The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments.

As noted in Section 4.3.5. the use of granulocyte colony-stimulating factor (G-CSF) primary prophylaxis is **REQUIRED** for all patients in this study during all cycles, with dosing per institutional guidelines. All patients will receive herpesvirus prophylaxis throughout the treatment with Polatuzumab Vedotin

Figure 2 Schematic of Polatuzumab Vedotin plus R-CHP Regimen **Cycles 1-6**



Prednisone, 100 mg/day on days 1 through 5

Rituximab, 375 mg/m^2

Polatuzumab 1.8 mg/kg

Cyclophosphamide, 750 mg/m^2

Doxorubicin, 50 mg/m^2

Intrathecal Methotrexate 12mg on either day 1, 2 or 3 of each cycle

Neulasta/Udenyca 6mg on day 3 or Neupogen 300-480 mcg daily for 5-10 days

Notes: Order of administration on Day 1 of each cycle will be: first prednisone, second rituximab, and third polatuzumab vedotin. Subsequent infusions of cyclophosphamide, and doxorubicin should be administered according to institutional preference. Neulasta or Neupogen will be administered on Day 3 of each cycle.

Rituximab may be split between Day 1 and Day 2 per Section 4.2.3.2. On Cycle 1, polatuzumab vedotin may be administered on Day 2 per investigator preference due to the longer infusion times for the first dose of rituximab and polatuzumab vedotin. In this instance, cyclophosphamide, and doxorubicin may be administered on Day 1, and polatuzumab vedotin may be administered on Day 2 after prednisone.

4.2.3. Study Treatment Formulation, Temperature Conditions, Packaging, and Handling

4.2.3.1 Polatuzumab Vedotin

The dose of polatuzumab vedotin for each patient will be 1.8 mg/kg.

The study drug is supplied in 20-cc single use glass vials with 20 mm stoppers. Each drug product vial delivers 140 mg [7.0 mL] of study drug after reconstitution with 7.2 mL sterile water for injection (SWFI). Upon reconstitution with 7.2 mL of SWFI, the concentration of Polatuzumab Vedotin is 20 mg/mL in a solution containing sodium succinate, sucrose, and polysorbate-20 at pH 5.3. Density of study drug following reconstitution is 1.02 g/mL.

Vial Storage Condition and Precautions:

- Store at 2°- 8°C (36°F–46°F).
- Do not freeze.
- Do not shake.
- Protect from light.
- For single use only.
- Do not use beyond expiration date

Dose solutions should be prepared in an IV infusion bag containing 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose and constructed with product contacting materials of polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), and/or polypropylene (PP).

Equipment Required for Infusion:

Do not use infusion bags containing other diluents (e.g.Ringers' solution, etc.).

Use a PVC, PO, PE, PP, polyurethane (PU), or polybutadiene (PBD) infusion line equipped with a 0.2 or 0.22 µm polyethersulfone (PES) or polysulfone (PSU) filter.

Reconstitution of the drug product must occur under appropriate aseptic conditions in accordance with local regulations and institutional policy, as the study drug contains no preservatives.

Reconstitution Instructions:

- Reconstitute immediately before dilution
- More than one vial may be needed for a full dose. Calculate the dose, the total volume of reconstituted Polatuzumab solution required, and the number of Polatuzumab vials needed.
- Reconstitute each 140 mg Polatuzumab vial by using a sterile syringe to slowly inject 7.2 mL of Sterile Water for Injection, USP, with the stream directed toward the inside wall of the vial to obtain a concentration of 20 mg/mL of polatuzumab vedotin-piiq.
- Swirl the vial gently until completely dissolved. Do not shake.
- Inspect the reconstituted solution for discoloration and particulate matter. The reconstituted solution should appear colorless to slightly brown, clear to slightly opalescent, and free of visible particulates. Do not use if the reconstituted solution is discolored, is cloudy, or contains visible particulates. Do not freeze or expose to direct sunlight.
- If needed, store unused reconstituted Polatuzumab solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 48 hours or at room temperature (9°C to 25°C, 47°F to 77°F) up to a maximum of 8 hours prior to dilution. Discard vial when cumulative storage time prior to dilution exceeds 48 hours.

Dilution

- Dilute polatuzumab vedotin-piiq to a final concentration of 0.72–2.7 mg/mL in an intravenous infusion bag with a minimum volume of 50 mL containing 0.9% Sodium Chloride Injection, USP, 0.45% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.
- Determine the volume of 20 mg/mL reconstituted solution needed based on the required dose.
- Withdraw the required volume of reconstituted solution from the Polatuzumab vial using a sterile syringe and dilute into the intravenous infusion bag. Discard any unused portion left in the vial.

- Gently mix the intravenous bag by slowly inverting the bag. Do not shake.
- Inspect the intravenous bag for particulates and discard if present.
- If not used immediately, store the diluted Polatuzumab solution as specified in in the table below. Discard if storage time exceeds these limits. Do not freeze or expose to direct sunlight.
- Limit transportation to 30 minutes at 9°C to 25°C or 12 hours at 2°C to 8°C (refer to instructions below). The total storage plus transportation times of the diluted product should not exceed the storage duration specified as below:

Diluent Used to Prepare Solution for Infusion	Diluted Polatuzumab Vedotin Solution Storage Conditions*
0.9% Sodium Chloride Injection, USP	Up to 24 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
0.45% Sodium Chloride Injection, USP	Up to 18 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
5% Dextrose Injection, USP	Up to 36 hours at 2°C to 8°C (36°F to 46°F) or up to 6 hours at room temperature (9 to 25°C, 47 to 77°F)

* To ensure product stability, do not exceed specified storage durations

Agitation stress can result in aggregation. Limit agitation of diluted product during preparation and transportation to administration site. Do not transport diluted product through an automated system (e.g., pneumatic tube or automated cart). If the prepared solution will be transported to a separate facility, remove air from the infusion bag to prevent aggregation. If air is removed, an infusion set with a vented spike is required to ensure accurate dosing during the infusion.

- No incompatibilities have been observed between Polatuzumab and intravenous infusion bags with product-contacting materials of polyvinyl chloride (PVC) or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP). No incompatibilities have been observed with infusion sets or infusion aids with product-contacting materials of PVC, PE, polyurethane (PU), polybutadiene (PBD), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU), fluorinated ethylene propylene (FEP), or

polytetrafluorethylene (PTFE), or with filter membranes composed of polyether sulfone (PES) or polysulfone (PSU).

Administration

- Administer Polatuzumab as an intravenous infusion only.
- Polatuzumab must be administered using a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein-binding in-line or add-on filter (0.2- or 0.22-micron pore size) and a catheter.
- Do not mix Polatuzumab with or administer as an infusion with other drugs.

Determination of Patient's weight: The total dose of Polatuzumab Vedotin for each patient will depend on the patient's body weight at the screening assessment (within 28 days of Cycle 1, Day 1).; If the patient's weight within 96 hours prior to Day 1 of a given treatment cycle > 10% from the weight obtained during screening, the new weight should be used to calculate the dose. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments. All subsequent doses should be modified accordingly. Dose recalculation for polatuzumab vedotin for weight changes
<10% are allowed at investigator discretion.

Dose solution preparation: Dose solution preparation must occur under appropriate aseptic conditions in accordance with local regulations and institutional policy, as the Polatuzumab Vedotin contains no preservatives.

Calculate the appropriate volume of undiluted study drug to the infusion bag using the equations below.

[Required dose (mg)] = [Patient weight (kg)] x [Dose per

kilogram (mg/kg)]

$$[Required\ volume\ (mL)] = \frac{[Required\ dose\ (mg)]}{20\ ^{mg}/_{mL}}$$

As an example, a 72 kg patient at the 1.8 mg/kg dose level would require a dose of 130 mg. The required volume of reconstituted drug product would be 6.5 mL in this

example.

Please note: Any deviation of the actual dose from the calculated dose by more than ± 5% is considered a protocol deviation.

Use the patient-specific required dose to select an appropriate size infusion bag to ensure that the final concentration of Polatuzumab Vedotin in the bag is between 0.72 mg/mL and 2.70 mg/mL. Use the bag's labeled volume to calculate concentration (ignore overfill).

Required Polatuzumab Vedotin Dose (mg)	Recommended IV Infusion Bag Volume (mL)
<72	50
72-270	100
>270	250

Using a new syringe and needle, withdraw the required volume of the reconstituted drug product from the vial, slowly add the required volume of drug product to the IV bag, and gently mix the IV bag by slowly rotating the bag. Do not shake. Inspect the bag for particulates and discard if present.

Dose Solution Handling and Storage: Do not shake or freeze infusion bags containing dose solution. Protect from direct sunlight. The reconstituted Polatuzumab Vedotin drug product and the dose solution should be used immediately to limit product degradation and microbial growth in case of potential accidental contamination.
If not used immediately, the reconstituted study drug solution may be stored refrigerated at 2-8°C (36-46°F) for up to 24 hours prior to dose solution preparation. Within this 24-hour storage period, the reconstituted study drug solution may be temporarily held at 9-25°C (47-77°F) up to a maximum of 4 hours. The reconstituted drug solution should be discarded if the cumulative storage time prior to the preparation of the dose solution exceeds 24 hours.

Similarly, the dose solution (resulting from dilution of the reconstituted product into an IV bag) may also be stored refrigerated at 2-8°C (36-46°F) for up to 24 hours prior to administration. Within this 24-hour storage period, the dose solution may be temporarily held at 9-25°C (47-77°F) up to a maximum of 4 hours. The dose solution should be discarded if the cumulative storage time prior to administration exceeds 24 hours.

Agitation stress can result in aggregation. Limit agitation of the dose solution during preparation and transportation to administration site. Transporation of the dose solution using an automated system (e.g. pneumatic tube or automated cart) have not been assessed. If transportation using automated system is unavoidable, site should be aware that their use may increase the risk for protein aggregation. If the dose

solution will be transported through automated system or to a separate facility, remove air from the infusion bag to reduce the risk for aggregation. If air is removed, an infusion set with a vented spike is required to ensure accurate dosing during the infusion. Limit transportation to 30 minutes at 9°C to 25°C or 12 hours at 2°C to 8°C. The total storage plus transportation times of the dose solution should not exceed the storage durations as indicated above.

Additional Instructions and Information: No incompatibilities have been observed between Polatuzumab Vedotin and IV infusion bags with product contacting materials of polyvinyl chloride (PVC), or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP). In addition, no incompatibilities have been observed with infusion sets or infusion aids with product contacting materials of PVC, PE, polyurethane (PU), polybutadiene (PBD), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), fluorinated ethylene propylene (FEP), polytetrafluorethylene (PTFE), polyether urethane (PEU), and with filter membranes composed of polyether sulfone (PES) or polysulfone (PSU). The use of administration items constructed of other product-contacting materials is not recommended.

Compatibility between Polatuzumab Vedotin and closed system transfer devices (CSTDs) or needle free transfer devices has not been assessed. If CSTDs or needle free transfer devices must be used to comply with site regulations, the site should be aware that their use may lead to the introduction of particles and may not allow the withdrawal of the labeled quantity of drug from the vial. Sites should perform a thorough visual inspection of the IV bag for particulates. In addition, sites must use a 0.2 or 0.22 µm polyethersulfone (PES) or polysulfone (PSU) filter during infusion. The preparation should be discarded if particulates are observed in the IV bag.

A dedicated infusion line and catheter should be used for the administration of Polatuzumab Vedotin. The compatibility of Polatuzumab Vedotin with other drugs as well as in-dwelling catheters such as peripherally inserted central catheters (PICCs) or other central venous access devices (CVADs) has not been established. If the treating health care provider determines that the use of a dedicated infusion line and catheter is not feasible, infusion lines and catheters must be flushed before and after administration of Polatuzumab to ensure that Polatuzumab does not contact other drug solutions.

Drug administration and pre-treatment recommendation: For Cycles 1-6, polatuzumab vedotin should be administered after the prednisone and rituximab components of R-CHP have been administered, as infusion reactions due to rituximab are typically more common than those for polatuzumab vedotin. The initial dose will be administered to patients who are well hydrated over 90 (± 10) minutes. Premedication (e.g., 500–1000 mg of oral acetaminophen or paracetamol and 50–100 mg diphenhydramine as per institutional standard practice) may be administered to an individual patient before administration of polatuzumab vedotin. Administration of

corticosteroids is permitted at the discretion of the treating physician. If infusion related reactions (IRRs) are observed with the first infusion in the absence of premedication, premedication must be administered before subsequent doses.

The polatuzumab vedotin 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. For infusion rate escalation after infusion related reactions, subsequent cycle of Polatuzumab Vedotin should be infused over 90 minutes. If prior infusions have been well tolerated, subsequent doses of polatuzumab vedotin may be administered over 30 (± 10) minutes, followed by a 30-minute observation period after the infusion.

Any dose modification should be noted on the Polatuzumab Vedotin Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.2.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4.1.

4.2.3.2 Rituximab

Rituximab 375 mg/m^2 will be administered by IV infusion in combination with polatuzumab vedotin, as outlined in Section 4.2. Rituximab will be administered on Day 1 of Cycles 1–6. No dose modifications of rituximab are allowed. Rituximab biosimilar will be allowed.

The patient's body surface area (BSA) calculated at screening should be used to calculate the dose of rituximab throughout the study unless the patient's weight increases or decreases by $>$10% from screening, in which case BSA should be recalculated and used for subsequent dosing. In obese patients, there is no BSA cap and actual body weight, not adjusted weight, is recommended. Empiric dose adjustment for obese patients (obesity defined as body mass index $\geq$30, as measured in kilograms divided by meters squared) may be implemented per institutional guidelines.

The rituximab administration should be completed at least 30 minutes (during cycle 1 and 15 minutes for subsequent cycles) before administration of other study treatments. The infusion of rituximab may be split over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). Administration of rituximab may be continued on the following day, if needed, for patients who experience an adverse event during the rituximab infusion. If a dose of rituximab is split over 2 days, both infusions must occur with appropriate premedication and at the first infusion rate (see Table 1).

All rituximab infusions should be administered to patients after premedication with oral acetaminophen (e.g., 650–1000 mg) and an antihistamine such as diphenhydramine hydrochloride (50–100 mg) 30–60 minutes before starting each infusion (unless contraindicated). An additional glucocorticoid (e.g., 100 mg IV prednisone or prednisolone or equivalent) is 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.

Rituximab infusions will be administered according to the instructions in Table 1. If a patient tolerates the first cycle of study treatment without significant infusion reactions, rituximab may be administered as rapid infusion in accordance with local institutional guidelines.

During the first cycle of treatment, rituximab must be administered to patients in a setting where full emergency resuscitation facilities are immediately available. Patients should be under close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Section 5.1.4.3

Rituximab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps (such as the Braun Infusomat Space) should be used to control the infusion rate of rituximab. Administration sets with polyvinyl chloride (PVC), polyurethane (PUR), or polyethylene (PE) as a product contact surface and IV bags with polyolefine, polypropylene (PP), PVC, or PE as a product contact surface are compatible and can be used. Additional in-line filters should not be used because of potential adsorption. The in-line filter used for the administration of polatuzumab vedotin should not be used for the administration of rituximab. Refer to the specific package inserts for preparation, administration, and storage conditions.

After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥2 hours in order to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed, or the central venous catheter may be de-accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed, or the central venous catheter may be de-accessed.

Table 1. Administration of First and Subsequent Infusions of Rituximab

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/hr 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 the reaction resolves, 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, 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/hr 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 the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate used at the time the reaction occurred).

Any dose modification should be noted on the Rituximab Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.2.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4.1.

4.2.3.3. Cyclophosphamide, Doxorubicin, and Prednisone Dosage and Administration

CHP chemotherapy consists of cyclophosphamide and doxorubicin administered via IV and oral prednisone. Doxorubicin and cyclophosphamide should be administered after both rituximab and polatuzumab vedotin infusions.

The dosages are based on the standard CHOP doses:

- Cyclophosphamide 750 mg/m_2 administered IV on Day 1 of Cycles 1-6
- Doxorubicin 50 mg/ m^2 administered IV on Day 1 of Cycles 1-6
- Prednisone 100 mg/day PO on Days 1 through 5 of each Cycle 1-6

  Note: Prednisone may be replaced with prednisolone (100 mg/day) or IV methylprednisolone (80 mg/day). Hydrocortisone may not be used as a substitute.

If glucocorticoid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, prednisone 100 mg or equivalent could be given for a maximum of 13 days as a prephase treatment, but all tumor assessments must be completed prior to starting glucocorticoid treatment.

Refer to the specific package inserts for preparation, administration, and storage guidelines. Cyclophosphamide is stored at 25C or below. Cyclophosphamide is available in 3 vial strengths (2 gm, 1 gm, and 500 mg). Use sterile water to reconstitute vial per package directions. Doxorubicin is stored at 2-8C with 2 different vial strengths. Refer to the specific package inserts for preparation, administration, and storage guidelines. BSA may be capped at 2 m2 per institutional standards. If CHP is started later than Day 1 of the cycle, then planned Day 1 of the next cycle should be calculated from the day when CHP was actually initiated, in order to maintain the regular chemotherapy interval of 21 days.

For details regarding storage, handling and formulation of Cyclophosphamide, Doxorubicin and Prednisone, please refer it package insert and institutional standards.

4.2.3.4. Premedications

Patients should receive premedications as outlined in Table 2.

Table 2. Premedication for Rituximab and Polatuzumab Vedotin

Timepoint	Patients who require pre-medication	Pre-medication	Administration
Cycle 1, Day 1	All patients	• Corticosteroid	Complete ≥ 1 hour prior to rituximab infusion.
		• Anti-histamine • Analgesic/Antipyretic	Administer ≥ 30 minutes prior to rituximab infusion; may be administered to patients prior to administration of any polatuzumab vedotin as well.
Cycles 2 and beyond, Day 1	Patients with no IRR during the previous infusion	• Corticosteroid	Complete ≥ 1 hour prior to rituximab and polatuzumab vedotin infusion.
		• Antihistamine drug • Analgesic/Anti-pyretic	Administer ≥ 30 minutes prior to infusion. These may be omitted at the investigator's discretion.

	Patients with Grade 1 or 2 IRR during the previous infusion	• Corticosteroid	Complete ≥ 1 hour prior to rituximab and polatuzumab vedotin infusion.
		• Antihistamine drug • Analgesic/Anti-pyretic	Administer ≥ 30 minutes prior to rituximab and/or polatuzumab vedotin infusion.
	Patients with Grade 3 IRR, wheezing, urticaria, or other symptoms of anaphylaxis during the previous infusion Patients with bulky disease	• Corticosteroid	Complete ≥ 1 hour prior to rituximab and/or polatuzumab Vedotin infusion.
		• Antihistamine drug • Analgesic/anti-pyretic	Administer ≥ 30 minutes prior to rituximab and/or polatuzumab Vedotin infusion.

4.2.4. Investigational Medicinal Product Accountability

All investigational medical products (IMPs) required for completion of this study (polatuzumab vedotin) will be provided by Roche/Genentech 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.

Rituximab Cyclophosphamide Adriamycin and Prednisone (RCHP) will be provided by the institutions as standard of care therapy. A refrigerator log to maintain appropriate storage conditions will be maintained by the site. Any temperature excursions should be reported to the sponsor.

4.3. CONCOMITANT THERAPY

4.3.1. Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study treatment completion visit, which is 30 (±5) days after the last dose of study treatment. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients may continue to use oral contraceptives, hormone-replacement therapy, or other maintenance therapies.

MMAE is a substrate of the cytochrome P450 (CYP450) enzymes, specifically CYP3A. Published data suggest that MMAE is neither an inhibitor nor inducer of CYP3A. Patients who are receiving strong CYP3A inhibitors should be closely monitored for adverse reactions when given polatuzumab vedotin (Han et al. 2013).

Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator. Other than the prednisone given as study treatment and prednisone that may be given as pre-phase treatment at the discretion of the treating investigator physician (see Section 4.2.3.4.), corticosteroids may be used only for the treatment of conditions other than lymphoma (e.g., asthma).

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-

associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and a_2-adrenergic agonists).

IMPORTANT NOTE*: The use of Evusheld or other post-exposure anti-viral medications against COVID19 does not affect study eligibility. Patients who have received Evusheld can be enrolled and patients who are already on study who receive Evusheld can remain on study. Receipt of Evusheld during or after study treatment will be documented. To capture side effects associated with individual agents, we would advise to maintain at least 1 week of gap between Evusheld and chemotherapeutic agents administration if possible. As new agents become available for patients, the study team will discuss best practices for administration of these agents and provide general guidelines with consideration for the integrity of the protocol.*

4.3.2. CNS Prophylaxis

CNS prophylaxis with intrathecal methotrexate 12 mg as CNS prophylaxis on day 1, 2 or 3 of each cycle of therapy is required and its use must be documented in the eCRF. CNS prophylaxis using systemic IV methotrexate (e.g., 1 g/m2 per cycle) is not permitted.

4.3.3. Prophylaxis for Hemorrhagic Cystitis

Patients should be adequately hydrated before and after cyclophosphamide administration and should be instructed to void frequently. Mesna may be used as prophylaxis according to institutional practice.

4.3.4. Transfusions for cytopenias

Patients may receive supportive platelet and blood transfusions per institutional guidelines once on active study therapy

4.3.5. Treatment and Prophylaxis of Neutropenia

G-CSF is required as primary prophylaxis in each cycle of therapy. Dosing of G-CSF should follow each site's institutional standards or may be at the investigator's discretion.

For patients who develop neutropenia despite prophylaxis, G-CSF is not routinely recommended for the treatment of uncomplicated neutropenia. However, G-CSF may be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors predictive of poor clinical outcomes (Smith et al. 2015).

4.3.6. Premedications before Rituximab

All rituximab infusions should be administered to patients after premedication. The

following premedication is required before rituximab therapy:

- Acetaminophen/paracetamol (650–1000 mg) orally at least 30–60 minutes before the start of all infusions
- Antihistamine, such as diphenhydramine (25–50 mg), approximately 30–60 minutes before the start of each infusion (unless contraindicated)

On Cycle 1 Day 1, it is recommended that glucocorticoids (e.g., 100 mg prednisone or prednisolone or equivalent) be given within 12 hours as pre-medication. 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.

4.3.7. Premedication for Patients at High Risk for Tumor Lysis Syndrome

Patients with high tumor burden and considered by the investigator to be at risk for tumor lysis should also receive tumor lysis prophylaxis prior to the initiation of treatment. Patients should be well hydrated. Starting 1–2 days prior to the first dose of study treatment, it is desirable to maintain a fluid intake of approximately 3 L/day. In addition, all patients with high tumor burden and considered to be at risk for tumor lysis should be treated with 300 mg/day of allopurinol orally or a suitable alternative treatment (i.e., rasburicase), starting 48–72 hours prior to Cycle 1 Day 1 of treatment and hydration. Patients should continue to receive repeated prophylaxis with allopurinol if deemed appropriate by the investigator and adequate hydration prior to each subsequent cycle of treatment.

4.3.8. Prophylaxis for Infections

All patints will receive herpesvirus prophylaxis as per institutional standards throughout the treatment with Polatuzumab Vedotin. Anti-infective prophylaxis for viral, fungal, bacterial, is permitted and should be instituted per institutional practice or investigator preference based on individual patient risk factors. All anti-infective prophylaxis used should be recorded appropriately in the eCRF.

4.3.9. Monitoring and Treatment for Hepatitis B Reactivation

Patients who are both HBsAg negative and anti-HBc positive may be included in this study. These patients should have HBV DNA levels obtained monthly during the study and for at least 12 months after the last cycle of therapy by means of real time PCR with the use of an assay that has a sensitivity of at least 10 IU/mL.

If the HBV-DNA assay becomes positive and is above the World Health Organization's (WHO) cutoff of 100 IU/mL, study treatment will be held, and the patient should be treated (for at least 1 year after the last dose of rituximab) with an appropriate nucleoside analogue and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume study treatment once HBV DNA levels decrease to undetectable levels.

If the HBV DNA assay becomes positive and is ≤100 IU/mL, the patient should be retested within 2 weeks. If the assay is still positive, study treatment will be held, and the patient should be treated with an appropriate nucleoside analogue (for at least 1 year after the last dose of rituximab) and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume study treatment once the HBV DNA levels decrease to undetectable levels.

If a patient's HBV DNA level exceeds 100 IU/mL while the patient is receiving anti-viral medication, study treatment will be permanently discontinued (see Section 5.1.4, 7).

4.3.10. Other Concomitant Medications

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards, including the use of growth factors (e.g., erythropoietin), if clinically indicated.

Anti-emetic therapy may be instituted for any patient if clinically indicated. Systemic steroid therapy will not be allowed either during or within 7 days before the first dose of study treatment with the exception of the following:

- Inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease (COPD)
- Pre-medication before rituximab or polatuzumab vedotin
- Topical steroids
- Stable replacement corticosteroid therapy for an inherited or acquired deficiency
- Ongoing corticosteroid use for lymphoma symptom control (13 days of prednisone is allowed)

4.3.11. Prohibited Therapy

Treatment with other concomitant anti-tumor agents not defined in this protocol as study treatment, radiotherapy, or other concurrent investigational agents of any type will result in withdrawal of patients from study treatment.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy, other than intrathecal chemotherapy for CNS prophylaxis
- Immunotherapy or immunosuppressive therapy, other than study treatments
- Radioimmunotherapy
- Hormone therapy, other than contraceptives, stable 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
- Any therapy (other than intrathecal CNS prophylaxis) intended for the treatment of

lymphoma whether it is approved by the European Medicines Agency (EMA) or the U.S. Food and Drug Administration (FDA) or is experimental

- Radiotherapy

4.3.12. Immunizations

Patients who participate in this study may not receive either primary or booster vaccinations with live virus vaccines for at least 28 days before initiation of rituximab, at any time during study treatment, or until B-cell recovery. 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 before study therapy.
Patients who require the use of any of these agents will be discontinued from study treatment.

4.3.13. Use of SARS-CoV-2 vaccines in patients who are receiving Polivy® (polatuzumab vedotin-piiq).

As of January 22, 2021, there is insufficient experience with the use of the SARS-CoV-2 mRNA vaccine in patients receiving Polivy.1 The decision to administer a SARS-CoV-2 mRNA vaccine should be individualized based on a patient's SARS-CoV-2 infection/complication risk, the general condition of the patient, the severity and seriousness of the underlying disease/condition for which the patient is receiving Polivy as well as the epidemiology of COVID-19 in the patient's geographical location. SARS-CoV-2 mRNA vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance.

Based on the published mechanism of action of the mRNA technology based SARS-CoV-2 vaccines and the known mechanism of action of Polivy, there is no scientific rationale to expect that the mRNA based SARS-CoV-2 vaccines will affect the efficacy or safety of Polivy.2 Vaccine studies have not been performed in patients treated with Polivy. Studies of traditional non-live vaccines in patients receiving rituximab show a diminished antibody response to those vaccines (influenza, varicella zoster, hepatitis B, pneumocccus, hemophillus influenzae B, tetanus). Similar attenuation of humoral immune response to vaccines is also expected in patients treated with Polivy.1
Based on the data available to date regarding the adverse events reported in patients enrolled in the COVID-19 vaccines trials, a potential for overlapping side effects with Polivy should be considered.3
Per American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO) and other organizations' recommendation, the oncology patients can receive the currently available non-live vaccines. For patients enrolled in this particular study, per our institutional guidelines, administration of an authorized Covid-19 vaccine, as a

supportive care measure is acceptable. The use of investigational vaccines is not recommended.
• The timing of vaccination is at the discretion of the investigator.
• COVID vaccination will not affect patient's eligibility for the trial.
• Administration of COVID-19 vaccine, should be appropriately documented and must be recorded in the Prior and Concomitant Medications form in the eCRF.
• If a patient receives the concomitant COVID vaccine, please capture each dose, indicate the manufacturer of the vaccine, the date of vaccination, and if this is the first or second dose of the vaccine.
• Please refer to the respective prescribing information of the authorized COVID vaccines.
• Please record all adverse events, including their causalities, as well as noted laboratory abnormalities.
• There may be concurrent known adverse events-- such as fatigue, body ache, fever, nausea-- associated with the authorized COVID- vaccines and other components of drugs used in this trial.
• All causalities associated with the treatment emergent events should be reported according to the clinical discretion of the investigator.
• Based on our current limited clinical information, there are no known contraindications associated with PoV or R-CHP and the available authorized COVID- vaccines. Please also consider contacting the manufacturer of the SARS-CoV-2 mRNA vaccine for additional information.

Clinicians interested in further information regarding vaccines for COVID-19 for the general population and in the cancer care community may find the following websites useful:
https://www.cdc.gov/vaccines/covid-19/index.html (US Centers for Disease Control and Prevention)
https://www.nccn.org/covid-19/ (National Comprehensive Cancer Network)

Polivy and SARS-CoV-2 Vaccines References

1. Data on file (37qhcmn57te4v5geru3qi8eld0).

2. Pardi N, Hogan MJ, Porter FW, et al. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov. E-pub Date: ppublish April 2018. DOI # 10.1038/nrd.2017.243 .
https://www.ncbi.nlm.nih.gov/pubmed/29326426

3. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine [supplementary appendix appears online]. N Engl J Med. E-pub Date: [published online ahead of print] December 2020. DOI # 10.1056/NEJMoa2034577.
https://www.ncbi.nlm.nih.gov/pubmed/33301246

4.4. STUDY ASSESSMENTS

Unless otherwise stated, the baseline measurement for any given assessment will be

defined as the last value obtained before the first dose of study drug. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.4.1. Informed Consent Forms and Screening

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.4.2. Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies, reason for transplant ineligibility, 2016 WHO classification, current Ann Arbor stage, and procedures), ECOG performance status, reproductive status, smoking history, alcohol and drugs abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded. B-symptoms (i.e., weight loss, night sweats, or fever) will be assessed according to Appendix 1. Demographic data will include age, sex, and self-reported race/ethnicity.

4.4.3. Prognostic Indices

IPI clinical factors at diagnosis and at enrollment will be collected. Please see Appendix 6 6 for description of the IPI.

4.4.4. Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

As part of tumor assessment, physical examinations should include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly (clinical response assessment). While it is important that these findings are documented in the notes from the physical exam, we do not intend to capture this data on the CRFs

as the measurements are not reliable.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment [lymph nodes, liver, and spleen]). Clinical assessments of peripheral neuropathy should be performed at screening, at Day 1 of each cycle, and at the treatment completion visit and recorded on the appropriate eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.4.5. Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Weight, height, and BSA will also be recorded. Height and BSA are required at screening only, unless there has been $>10\%$ change in body weight since the last BSA assessment, in which case BSA should be recalculated and documented in the eCRF.

During the administration of polatuzumab vedotin, vital signs should be assessed before 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 following completion of dosing at Cycle 1 and 30 (± 10) minutes following completion of dosing in subsequent cycles.

During the administration of rituximab in Cycle 1, vital signs are to be obtained before infusion of rituximab, then 15 minutes after the start of infusion. Vital signs will be measured approximately every 15 (± 5) minutes for 90 minutes, then every 30 (± 10) minutes until 1 hour after the end of the infusion. During administration of rituximab in subsequent cycles, vital signs are to be recorded before infusion of rituximab, then 15 minutes after the start of infusion, and approximately every 30 (± 10) minutes until 1 hour after the end of infusion.

4.4.6. Tumor and Response Evaluations

All evaluable or measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. An Independent Review Committee with the participation of the study Principal Investigator and other participating site investigator, during interim analysis and at the completion of the study, will assess responses on the basis of physical examinations, CT scans, PET-CT scans, and bone marrow examinations using the Lugano Response Criteria (Cheson et al. 2014).

Radiographic Assessments

PET-CT scans should include skull-base to mid-thigh. Full-body PET-CT 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 regulatory 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, (e.g., patients with contrast allergy or impaired renal clearance), 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 in conjunction with diagnostic CT scans will be obtained in this study at screening, interim assessment (between cycle 3 day 15 and cycle 4 day 15), and at the end of treatment (6-8 weeks after the last dose of treatment). If disease progression upon completion of therapy is identified, confirmation by PET-CT is recommended. If local practice prohibits obtaining both assessments after Cycle 4, PET-CT alone (preferred) or CT alone may be obtained at this time. The Lugano Response Criteria (Appendix 2) will be used to assess overall response to study treatment.
The same radiographic assessment modality should be used for all response evaluations to ensure consistency across different time points.

At all times during the study, diagnosis of disease progression based on clinical examination must be confirmed on CT scan (or MRI scan if CT scan is contraindicated) as soon as feasible (maximum, within 30 days) and prior to initiation of non–protocol specified anti-lymphoma therapy.

Bone Marrow Assessments

Bone marrow examinations are optional at screening for staging purposes in all patients dependent on physician discretion. Bone marrow examinations should include a biopsy for morphology and an aspirate for local hematology (optional if standard of care at the site).

Repeat bone marrow examinations are required in two circumstances:
If there was bone marrow infiltration at screening, then a subsequent bone marrow biopsy (trephine) at the primary response assessment visit is required for clinical response evaluation for all patients who may have achieved a CR. In patients with a PR and continued bone marrow involvement, a subsequent bone marrow examination may be required to confirm a CR at a later time point.

Any additional (unscheduled) bone marrow examinations performed during the study will be at the discretion of the investigator.

4.4.7. Laboratory, Biomarker, and Other Biological Samples

4.4.7.1. Local Laboratory Assessments

Samples for hematology, serum chemistry, pregnancy, hepatitis B and C serology will be analyzed at the study site's local laboratory. Laboratory samples may be obtained up to 72 hours (within 7 days for pregnancy testing) before start of study treatment administration on Day 1 of the treatment cycle.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (CBC with differential to include basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, monocytes, neutrophils, platelet count, red blood cell count, total white cell count).
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN/urea, creatinine, calcium, magnesium, phosphorus, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, uric acid/urate, hemoglobin A1c. HbA1c will be measured only at Screening and at Cycle 4 Day 1 and can be obtained in a non-fasting state. Only at screening, obtain beta-2 microglobulin.
- Lactate dehydrogenase (LDH)
- Coagulation: INR or PT, and PTT or aPTT
- Amylase
- HIV
- Viral serology:
  - Hepatitis B surface antibody (HBsAb), HbsAg, and total HbcAb
  - HBV-DNA by PCR if the patient is HbcAb positive
  - HCV antibody
  - HCV RNA by PCR if the patient is HCV antibody positive
- CSF assessment, as clinically indicated, for detection of CNS lymphoma
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test within 7 days before Cycle 1 Day 1 of study treatment. In addition, for women of childbearing potential, a serum or urine pregnancy test must be performed prior to study treatment on Day 1 of each subsequent cycle of study treatment (laboratory samples may be obtained up to 72 hours before start of study treatment administration on Day 1 of the treatment cycle). If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.

4.4.7.2. Central Pathology submission for correlative tissue evaluation

Tumor tissue samples and the corresponding pathology report, for retrospective central

confirmation of the diagnosis of DLBCL and for exploratory analyses. The specimen must contain adequate evaluable tumor cells (≥20% for excisional biopsy and ≥50% for core biopsy).

- Formalin-fixed paraffin-embedded tissue blocks are preferred over slides. Tissue blocks that are not formalin fixed will be accepted in countries that use a fixative other than paraformaldehyde, but information on the type of fixative should be included. If a tissue block is not available, a minimum of 15 serial, freshly cut, unstained slides accompanied by a tumor block punch may be sent. A tumor block or tumor block punch is required for construction of a tissue microarray.
- If archival tissue is unavailable or unacceptable according to above criteria, a pretreatment core needle, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

The sample should be shipped according to instructions provided in section 4.1.3. For sampling procedures, storage conditions, and shipment instructions, see section 4.1.3.

4.4.8. Electrocardiograms and Echocardiogram or MUGA

A resting 12-lead ECG is required at screening and as clinically indicated. ECGs for each patient should be obtained with the use of the same machine when possible. Interpretation of the ECG should be performed by a qualified investigator or sub-investigator.

Lead placement should be as consistent as possible. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation, should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Clinically significant events should be reported as adverse events.

For assessment of cardiac function (LVEF), an ECHO or MUGA scan should also be obtained at screening. An ECHO or MUGA scan may also be obtained as clinically indicated. During infusion of doxorubicin, ECG monitoring should be performed per clinical practice.

4.4.9. Timing of Study Assessments

4.4.9.1. Screening and Pretreatment Assessments

A signed ICF for participation in the study must be obtained before performing any study-specific screening tests or evaluations.

Screening and pretreatment tests and evaluations will be performed within 28 days

before first dose, unless otherwise specified. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days before first dose may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

See Appendix 1 for the schedule of screening and pretreatment assessments.

4.4.9.2. Assessments during Treatment

All assessments must be performed on the day of the specified visit unless a time window is specified in the schedule of assessments (see Appendix 1). Assessments scheduled on the day of study treatment administration should be performed before administration of study treatment, unless otherwise noted in the schedule of assessments.

See Appendix 1 for the schedule of assessments performed during the treatment period.

NOTE: participants with diabetes must have weekly comprehensive metabolic panels (including glucose) during the first 3 cycles of study treatment and will be counseled to ensure anti-diabetic medication adherence. The research nurse will ensure compliance with anti-diabetic medications and assist in monitoring blood glucose to keep levels below 300 mg/dL throughout study treatment.

4.4.9.3. Follow-Up Assessments

Month 0 in follow-up is considered to be the treatment completion visit.

4.4.9.3.1. Treatment Completion Visit

Patients who complete the study treatment period (defined as completion of six cycles of study treatment) or discontinue from the study treatment early (i.e., if they terminated treatment early because of an adverse event) will be asked to return to the clinic within 30 days (±5 days) after the last dose of study treatment for a treatment completion visit. The visit at which response assessment shows progressive disease may be used as the treatment completion visit.

See Appendix 1 for the schedule of assessments performed at the treatment completion visit.

4.4.9.3.2. Suspected Progression

Patients who demonstrate clinical concern for progression should be evaluated by appropriate scans as (described in section 4.4.6), laboratory assessments, and physical exam. This visit is to take place at any time when progression is suspected.

See Appendix 1 for the schedule of assessments performed at the time of suspected progression.

4.4.9.3.3. Primary Response Assessment Visit

All patients will be asked to return to the clinic for the primary response assessment visit. This visit is to take place between 6 to 8 weeks after the last dose of study treatment.

See Appendix 1 for the schedule of assessments performed at the primary response assessment visit.

4.4.9.3.4. Every 3-Month Visit until End of Study

For patients without disease progression, assessments will be performed every 3 months ±14 days after the treatment completion visit, until 5 years. Other assessments are indicated in Appendix 1. Disease Progression and No New Treatment

If response assessment shows PD during the follow-up period, subsequent visits will have assessments limited to recording of any new anti-lymphoma therapy, the occurrence of adverse events (per Section 5.2.), and survival. Diagnosis of disease progression based on clinical examination must be confirmed by CT scan as soon as possible (maximum, within 4 weeks) and prior to any new anti-lymphoma therapy. If no new treatment is started, the subject will be followed per the usual follow-up schedule.

4.4.9.3.5. Disease Progression and New Treatment

After a patient has PD during follow-up and starts a new anti-lymphoma therapy, contact will be made with patients by telephone on at least an annual basis for survival.

4.4.9.3.6. No Disease Progression and New Treatment

Patients who discontinue study treatment early because of adverse event and start a new anti-lymphoma therapy in the absence of PD should be followed according to the protocol schedule, including the *response assessments and the* reporting of adverse events until 30 days after the last dose of study drug (see Section 5.2.) unless they withdraw consent.

See the schedule of assessments provided in Appendix 1 for specified follow-up assessments.

4.4.9.3.7. Assessments at Unplanned Visits

See Appendix 1 for assessments that are required in the event of an unplanned visit.

4.5. PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.5.1. Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient.
- Patient non-compliance (i.e., consistent failure to show up for scheduled visits, consistent missed treatment, etc.)

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.5.2. Study Treatment Discontinuation

A patient must discontinue study treatment permanently if any of the following occurs:

- Grade 4 Infusion related reaction (IRR). The patient should be withdrawn from study treatment immediately and rituximab treatment should be permanently discontinued.
- Recurrence of Grade 3 IRR at re-challenge. Treatment should be permanently discontinued.
- Patients with infusion-related Grade ≥ 3 wheezing, hypoxia, or generalized urticaria must be permanently discontinued from study drug on the first occurrence.
- Grade ≥ 3 toxicity that does not resolve to Grade ≤ 2 or baseline value within 2 weeks after last dose and that has a reasonable possibility of being related to the administration of polatuzumab vedotin, or rituximab.
- Recurrent Grade 4 neutropenia with infection, despite G-CSF support
- Grade 4 neurotoxicity including peripheral neuropathy
- Grade 3 neurotoxicity that leads to a treatment delay of 14 days or more and does not improve to Grade ≤ 2 within 14 days
- Disease progression
- Any dose delay of ≥ 4 weeks
- Pregnancy
- Use of an anti-cancer therapy not required per protocol

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

In the event that a patient discontinues from study treatment early for reasons other than documented disease progression/relapse, that patient will proceed into the follow-up period until progression.

All patients will return to the clinic for an early treatment termination visit within 4-8 weeks after the last dose of study drug and should obtain tumor response assessments. Assessments should continue to follow the schedule outlined in Appendix 1 and Appendix 2.

4.5.3. Study and Site Discontinuation

The Sponsor 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.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference for Harmonisation (ICH) guideline for GCP
- No study activity (i.e., all patients have completed, and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1. SAFETY PLAN

Polatuzumab vedotin is not approved in front line setting in combination with R-CHP and is currently in clinical development; the entire safety profile is not known at this time. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

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, including serious adverse events, from Cycle 1 Day 1,

regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug. After this period, the Sponsor should be notified of any post-study SAEs or non-SAEs of special interest, regardless of attribution (see Section 5.2. for reporting details).

- Measurements of protocol-specified hematology and clinical chemistry laboratory values
- Measurements of protocol-specified vital signs
- Assessment of ECGs and physical findings on clinical physical examinations

5.1.1. Risks Associated with Polatuzumab Vedotin

The clinical safety profile of polatuzumab vedotin is based on clinical data obtained in the ongoing Phase I and Phase II studies. This profile is summarized in Section 1.2. On the basis of clinical data to date, the known and suspected risks are described below. Polatuzumab vedotin (170 mg/vial lyophilized) is currently in use in other clinical trials with an observed safety profile that is consistent with the known safety profile.

Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.4. Refer also to the Investigator's Brochure for complete and updated details.

5.1.1.1. Known Risks: Myelosuppression and Peripheral Neuropathy:

5.1.1.1.1 Myelosuppression: this is an identified risk that is a consolidation of three adverse drug reactions: neutropenia, thrombocytopenia, and anemia.

Neutropenia

Neutropenia and neutropenia-associated events (including febrile neutropenia) have generally been 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 for hematologic toxicities may be delayed or modified as described in Section 5.1.4. and Table 7. The use of G-CSF for neutropenia is described in Section 4.3.5.

Thrombocytopenia: thrombocytopenia is an adverse drug reaction of polatuzumab vedotin. It can occur in patients receiving polatuzumab vedotin as monotherapy and in combination with rituximab, obinutuzumab chemotherapy, atezolizumab, lenalidomide, or venetoclax. Grade 3−4 thrombocytopenia has been reported in patients treated with polatuzumab vedotin. Patients receiving polatuzumab vedotin should be regularly monitored with complete blood counts. Dose delays or modifications should be considered as outlined in the protocol for patients with Grade 3−4 thrombocytopenia. Transfusion support for thrombocytopenia can be provided in accordance with the local guidelines.

Anemia: anemia is an adverse reaction of polatuzumab vedotin. It can occur in patients

receiving polatuzumab vedotin as monotherapy or in combination with other chemotherapeutic agents. Grade 3−4 anemia has been reported in patients treated with polatuzumab vedotin. Patients receiving polatuzumab vedotin should be regularly monitored with complete blood counts. Transfusion support for anemia can be provided in accordance with the local guidelines.

5.1.1.1.2 Peripheral Neuropathy

Patients receiving polatuzumab vedotin may develop peripheral neuropathy, including peripheral sensory and/or motor neuropathy. These events have generally been reversible to varying degrees as much as available, but it is not known if full reversibility can be expected or predicted. Patients in clinical trials with polatuzumab vedotin should be monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, loss of balance, orthostatic hypotension, syncope, or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require a dose delay, change in dose, or discontinuation of treatment and should be managed according to the protocol. Study treatment dose and schedule modifications for peripheral neuropathy are described in Section 5.1.4. and Table 7. Supportive care measures may be implemented per investigator preference (e.g., gabapentin).

5.1.1.1.3 Infections

Infection is an identified risk (both serious and non-serious), and an adverse drug reaction (ADR) of polatuzumab vedotin. Serious, life threatening, or fatal infections, including opportunistic infections, such as pneumonia (including pneumocystis jirovecii and other fungal pneumonia), bacteremia, sepsis, herpes infection, and cytomegalovirus infection have been reported in patients treated with polatuzumab vedotin. Patients should be closely monitored during treatment for signs of bacterial, fungal, or viral infections. Anti-infective prophylaxis should be considered. Polatuzumab vedotin and any concomitant chemotherapy should be discontinued in patients who develop serious infections.

5.1.1.1.4 Polatuzumab Vedotin 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/anaphylactic reactions are rare after the first dose of a product, because they require prior sensitization. Patients with true allergic/anaphylactic reactions should not receive further doses of the product.

Mabs may also be associated with reactions that are clinically indistinguishable from true allergic/anaphylactic reactions, but that 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 pretreatment with various medications.

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

Because of the potential for infusion reactions with protein drugs, administration of polatuzumab vedotin will be performed in a setting ready with access to emergency equipment and staff who are trained to monitor and respond to medical emergencies. All patients will be monitored for infusion reactions during the infusions and immediately afterwards (for additional instructions on the monitoring and management of infusion reactions, see Section 5.1.4.3. and Table 6). Recommended management of suspected anaphylactic reactions during study drug infusions is provided in Appendix 4.
The initial dose of polatuzumab vedotin may be administered with premedication with acetaminophen/paracetamol, antihistamines, or corticosteroids per institutional standard practice at the discretion of the Investigator. Premedication should be used for subsequent doses if IRRs are observed in patients who receive their first dose of polatuzumab vedotin without premedications. Significant issues with polatuzumab vedotin IRRs have not been observed.

Similar considerations regarding infusion reactions are applicable for rituximab. Refer to Section 4.2.3.2 for additional information.

5.1.1.1.5 Gastrointestinal Toxicity

Gastrointestinal toxicities are among the most commonly reported adverse events in patients being treated with polatuzumab vedotin and include diarrhea, nausea, vomiting, constipation, and abdominal pain. These events have been responsible for dose modifications and drug discontinuation and are managed with standard-of-care treatment.

5.1.1.1.6 Summary of Adverse Drug Reactions Occurring in Patients with Previously Untreated DLBCL Treated with Polatuzumab Vedotin in Combination with R-CHP

Infections and Infestations: upper respiratory tract infection, pneumonia, urinary tract infection, herpes virus infection, sepsis, and cytomegalovirus infection.

Blood and Lymphatic System Disorders: neutropenia, anemia, febrile neutropenia, leukopenia, thrombocytopenia, lymphopenia, and pancytopenia.

Metabolism and Nutrition Disorders: decreased appetite, hypokalemia, hypoalbuminemia, and hypocalcemia.

Nervous System Disorders: neuropathy peripheral and dizziness.

Respiratory, Thoracic, and Mediastinal Disorders: cough, dyspnea, and pneumonitis.

Gastrointestinal Disorders: nausea, diarrhea, constipation, abdominal pain, and vomiting.

Skin and Subcutaneous Tissue Disorders: alopecia, rash, pruritis, skin infections, and dry skin.

Musculoskeletal Disorders: myalgia and arthralgia.

General Disorders and Administration Site Conditions: fatigue, mucositis, pyrexia, asthenia, peripheral edema, and chills.

Investigations: weight decreased, transaminases increased, and hypophosphatemia.

Injury, Poisoning, and Procedural: infusion related reaction.

5.1.1.2. Potential Risks Associated with Polatuzumab Vedotin

See the Investigator's Brochure for polatuzumab vedotin for full information.

Progressive Multifocal Leukoencephalopathy (PML): one case of PML has been reported with polatuzumab vedotin treatment. Patients should be monitored closely for new or worsening neurological, cognitive, or behavioral changes suggestive of PML. Polatuzumab vedotin and any concomitant chemotherapy should be held if PML is suspected and permanently discontinued if the diagnosis is confirmed.

Hepatic Toxicity (Hyperbilirubinemia, Transaminase [AST or ALT] Elevation)

Evidence exists of hepatic toxicity with similar ADCs using the cytotoxic agent MMAE in both nonclinical and clinical studies. This class effect is usually described as mild and reversible. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk.

5.1.1.2.1. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a risk if treatment with polatuzumab vedotin 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 taken. 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 $\geq$300 mg/day orally or a suitable alternative treatment [according to institutional practice] starting 12–24 hours before study treatment) and must be well hydrated before the initiation of study treatment at Cycle 1 Day 1. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration before each subsequent infusion,

as deemed appropriate by the investigator.

5.1.1.2.2. Immunogenicity

As with any recombinant antibody, polatuzumab vedotin may elicit an immune response and patients may develop antibodies against polatuzumab vedotin. Patients will be closely monitored for any potential immune response to polatuzumab vedotin. Appropriate screening, confirmatory, and characterization assays will be employed to assess ADAs before, during, and after the treatment with polatuzumab vedotin. Given the historically low immunogenicity rate of rituximab in patients with NHL, ADAs against rituximab will not be monitored in this study.

5.1.1.2.3. Reproductive Toxicity

Adverse effects on human reproduction and fertility are anticipated with the administration of polatuzumab vedotin given the mechanism of action of MMAE and the cytotoxic component of polatuzumab vedotin as a microtubule inhibitor.

No clinical studies assessing the reproductive and embryo-fetal toxicity of polatuzumab vedotin have been conducted to date. It is not known whether polatuzumab vedotin can cross the placenta or cause harm to the fetus when administered to pregnant women or whether it affects reproductive capacity. It is not known whether polatuzumab vedotin can be found in sperm.

5.1.1.2.4. Hyperglycemia

Hyperglycemia has been observed in patients treated with polatuzumab vedotin and with other ADCs that use the same vc-MMAE platform. Hyperglycemia has been reversible upon holding or discontinuing treatment of the ADCs and/or initiation or adjustment of standard-of-care anti-hyperglycemic medications.

Genotoxicity/Carcinogenicity (Myelodysplastic Syndrome)

MMAE, the cytotoxic component of polatuzumab vedotin, is a microtubule inhibitor targeting rapidly dividing cells and is expected to be carcinogenic. Patients who received chemotherapy with vincristine sulfate in combination with anticanceranti-cancer drugs known to be carcinogenic have developed second malignancies, although the contributing role of vincristine sulfate has not been determined.

Renal Toxicity (Increased Serum Creatinine)

Preliminary safety observations in clinical trials with ADCs using the same linker and MMAE have suggested that some patients experience reduction of renal function during clinical trials. Most events occurred in the setting of dehydration or other inciting illnesses.

Cardiac Arrhythmias

While not observed in the nonclinical GLP studies, several SAEs of cardiac toxicities have been experienced by patients receiving an ADC-vc-MMAE, which is in the same class as polatuzumab vedotin.

Ocular Toxicity

While not observed in nonclinical GLP studies, treatment-emergent AEs of ocular toxicities have been experienced by patients receiving antibody drugs with the same drug conjugate (ADC-vc-MMAEs) as polatuzumab vedotin.

Dysgeusia
While not observed in the nonclinical GLP studies, treatment-emergent AEs of dysgeusia or alteration of taste have been experienced by patients receiving ADC-vc-MMAEs which are in the same class as polatuzumab vedotin.

5.1.2 Risks Associated with Rituximab Therapy

See the Package Insert/Summary of Product Characteristics for rituximab for full information.

Possible Side Effects of Rituximab (Table Version Date: August 30, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Rituximab, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Anemia which may require blood transfusion • Nausea • Reaction during or following infusion of the drug • Chills, fever • Tiredness

5.1.2.1. Infusion-Related Reactions

Patients treated with rituximab are at risk for IRRs. Fatal infusion reactions within 24 hours of rituximab infusion can occur; approximately 80% of fatal reactions occurred with the first infusion. Severe reactions to rituximab typically occurred during the first infusion with time to onset of 30–120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

5.1.2.2. Tumor Lysis Syndrome

Patients treated with rituximab may be at risk for TLS. With rituximab treatment, acute renal failure, hyperkalemia, hypocalcaemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of rituximab in patients with NHL. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden confers a greater risk of TLS. For patients with evidence of TLS, rituximab should be discontinued, and the patient treated as clinically indicated.

5.1.2.3. Hepatitis B Reactivation

HBV reactivation with subsequent fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of rituximab treatment and approximately 1 month after the last dose.

Patients with chronic hepatitis B (HbsAg-positive) viral infection are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HbsAg-negative and anti-HbcAb-positive) are at a lower risk for reactivation. Patients who demonstrate evidence of reactivation while receiving an appropriate anti-viral therapy will be discontinued from study treatment.

5.1.2.4. Progressive Multifocal Leukoencephalopathy

Rare cases of progressive multifocal leukoencephalopathy (PML) have also been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications (Goldberg et al. 2002; Calabrese et al. 2007; Carson et al. 2009). In a review of 57 patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem cell or solid-organ graft rejection. The diagnosis of PML in any patient treated with rituximab is rare but should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic SCT. Most cases of PML were diagnosed within 12 months of the patient's last infusion of rituximab.

5.1.2.5. Cardiac Toxicity

Angina and cardiac arrhythmias have occurred with rituximab treatment and can be life-threatening. 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 with subsequent infusions of rituximab. Patients with pre-existing cardiac conditions, including angina and arrhythmias, and who have had recurrences of these events during rituximab therapy should be monitored throughout the infusion and in the post-infusion period.

5.1.2.6. Infection

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following completion of rituximab-based therapy. New or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, Varicella zoster virus, West Nile virus, and hepatitis B and C viruses.

5.1.2.7. Severe Mucocutaneous Reactions

Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (TEN). The onset of these reactions in patients treated with rituximab has varied from 1 to 13 weeks following rituximab exposure.

5.1.2.8. Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In postmarketing reports of rituximab, the mean time to documented gastrointestinal perforation was 6 days (range 1–77 days) in patients with NHL.

5.1.3. Risks Associated with Cyclophosphamide, Doxorubicin and Prednisone

Please see the Package Insert/Summary of Product Characteristics for Cyclophosphamide, Doxorubicin, and Prednisone for full information.

Possible Side Effects of **Cyclophosphamide** (Table Version Date: May 4, 2021)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require transfusion • Bruising, bleeding • Blood in urine • Nausea, vomiting, diarrhea, loss of appetite, pain in belly • Sores in mouth which may cause difficulty swallowing • Absence of menstrual period which may decrease the ability to have children • Hair loss, skin changes, rash, change in nails

Possible Side Effects of **Doxorubicin (Table Version Date: October 15, 2020)**

COMMON, SOME MAY BE SERIOUS In 100 people receiving Doxorubicin, more than 20 and up to 100 may have:
• Nausea, vomiting • Red colored urine, saliva, or sweat • Hair loss

Possible Side Effects of **Prednisone (Table Version Date: February 4, 2022)**

COMMON, SOME MAY BE SERIOUS In 100 people receiving Prednisone, more than 20 and up to 100 may have:
• High blood pressure which may cause headaches, dizziness, blurred vision • Swelling of the body, tiredness, bruising • In children and adolescents: decreased height • Increased appetite and weight gain in the belly, face, back and shoulders • Pain in belly • Loss of bone tissue • Difficulty sleeping • Mood swings • Skin changes, acne

5.1.4. Management of Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 7.

Additional guidelines are provided in the subsections below.

5.1.4.1. Dose Delays and Dose Modifications

Patients should be assessed clinically for toxicity before each dose using NCI CTCAE v5.0 unless otherwise stated. These guidelines pertain to dose delays and modifications based on physical examination findings, observed toxicities, and laboratory results obtained within 72 hours before study treatment administration. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable. The determination of all dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment in consultation with the Medical Monitor and with the approval of the Medical Monitor.

These guidelines pertain to dose delays and modifications based on physical examination findings, observed toxicities, and laboratory results obtained within 72 hours before study treatment administration. Guidelines for dose delays and modifications of polatuzumab vedotin, cyclophosphamide and doxorubicin are shown in Table 3, Table 4, and Table 5. The determination of all dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment in consultation with and with the approval of the Medical Monitor.

Cyclophosphamide and Doxorubicin doses may be reduced as outlined in Table 4 and Table 5, respectively. Cyclophosphamide or doxorubicin may be reduced separately; that is, one or both agents may be reduced in 25%-50% increments per investigator preference. Cyclophosphamide and doxorubicin doses may be re-escalated (even to the full dose) with the approval of the Medical Monitor.

The dose of polatuzumab vedotin and chemotherapy (cyclophosphamide or doxorubicin) can be reduced stepwise to a maximum of two levels for management of drug-related toxicities. If further dose reduction is indicated after two dose reductions, the patient must discontinue the specific study drug but may continue treatment with the remaining study drugs at the investigator's discretion in consultation with the Medical Monitor.

The administration of polatuzumab vedotin and R-CHP should be delayed for the same time frame; that is, all study drugs should be delayed for the same time frame so that they are all given together beginning on Day 1 of the same cycle.

Table 3 Recommended steps of Dose Reduction for Polatuzumab Vedotin

Dose level	Polatuzumab Vedotin
Starting dose	1.8 mg/kg per cycle
First dose reduction	1.4 mg/kg per cycle
Second dose reduction	1.0 mg/kg per cycle
Third dose reduction	Discontinue drug

Table 4 Recommended steps of Dose reduction for Cyclophosphamide

Dose level	Cyclophosphamide
Starting dose	100% of starting dose per cycle
First dose reduction	75%-50% of starting dose per cycle
Maximum dose reduction	50% of starting dose per cycle or discontinue drug
Subsequent dose reduction	Discontinue drug

Table 5 Recommended steps of Dose reduction for Doxorubicin

Dose level	Doxorubicin
Starting dose	100% of starting dose per cycle
First dose reduction	75%-50% of starting dose per cycle
Maximum dose reduction	50% of starting dose per cycle or discontinue drug
Subsequent dose reduction	Discontinue drug

5.1.4.2.Treatment interruptions and Schedule Modifications

Patients with DLBCL who have received Cycle 1 treatment may have the dosing schedule changed to a 28-day cycle if it is considered 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 of this type to the dosing schedule must be made in consultation with the Medical Monitor and have the approval of the Medical Monitor.

Study treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug (see Table 7). Aside from the withholding of polatuzumab vedotin for neuropathy per Table 7, study drugs withheld for >14 days because of toxicity should be discontinued, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. In this previously untreated curative setting, study treatments can continue with the remaining study drugs in the event one or more of the study drugs are discontinued.

Study treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption. 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 Cycles 2-6 are detailed below. Patients who are receiving study treatment and experience toxicities should undergo dose interruptions and reductions, per instructions in Table 7. All considerations of dose and schedule modifications should be discussed with and approved by the Medical

Monitor.

5.1.4.3. Non-Hematologic Toxicities

5.1.4.3.1. Infusion-Related Reactions and Anaphylaxis

Medications including epinephrine for SC injections, corticosteroids, diphenhydramine hydrochloride for IV injection, and resuscitation equipment should be available for immediate use during the first cycle of treatment. Management of infusion-related symptoms for rituximab are summarized in Table 6 according to the administration rates in Section 4.2.3.2. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE- mediated anaphylactic reaction, rituximab should be discontinued, and no additional drug should be administered. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued from study treatment. See Appendix 4 for recommended management of anaphylaxis.

Patients who experience rituximab-associated infusion-related temperature elevations of $>$38.5°C or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol (500−1000 mg) and/or H1- and H2- histamine receptor antagonists (e.g., diphenhydramine hydrochloride) and 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, epinephrine, and/or corticosteroids) as clinically indicated according to standard clinical practice. See Appendix 4 for recommended management of anaphylaxis.

Guidelines for the management of IRRs and anaphylaxis are detailed in Table 6.

Table 6 Management of Infusion-Related Symptoms: Rituximab and PoV

Infusion-Related Symptoms	Guidance
Grade 1-2	• Slow or hold infusion. • Give supportive treatment. [A] • Upon symptom resolution, may resume infusion-rate escalation at the investigator's discretion. • Note: For Grade 2 wheezing or urticaria, patient must be premedicated for any subsequent doses. If symptoms recur, the infusion must be stopped immediately, and study drug permanently discontinued.
Grade 3	• Discontinue infusion. • Give supportive treatment. [A] • Upon symptom resolution, may resume infusion-rate escalation, at investigator discretion. [B] • Note: If the same adverse event recurs with same 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, bronchospasm, or generalized urticaria at first occurrence, study drug must be permanently discontinued.
Grade 4	• Discontinue infusion immediately, treat symptoms aggressively, and permanently discontinue study drug.

IV = intravenous; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0

Refer to the NCI-CTCAE v5.0 scale for the grading of symptoms. Management of IgE-mediated allergic reactions should be as directed in the text following this table.

[A] Supportive treatment: Patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the previous 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 who require vasopressor support must be permanently discontinued from study drug.

[B] 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/hour every 30 minutes.

Table 7 Guidelines for Dose Delay or Modification of Polatuzumab Vedotin and R-CHP

Event(s)	Dose Delay or Modification
Grade 3 or 4 neutropenia on Day 1 of any Cycle with or without infection or fever [a] First delay	• Delay all study treatment. Treatment cannot be delayed for more than 2 weeks. • Administer growth factors *as appropriate*; (e.g., G-CSF for neutropenia as indicated and for all subsequent cycles). • If ANC recovers to $>1000/\mu L$ by Day 7 of the scheduled date for the next cycle, administer full dose of polatuzumab vedotin, and rituximab. • If ANC recovers to $>1000/\mu L$ after Day 7 of the scheduled date for the next cycle, Polatuzumab dose will be reduced to $1.4mg/m^2$ if growth factor support was administered per protocol. If a second occurrence is noted of >7 days, steps will be followed per section 5.1.4.1. • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose. Decisions must be made in consultation with and with approval of the Medical Monitor.
Recurrent Grade 3 or 4 neutropenia on Day 1 of any Cycle	• Delay doses of all study treatment. Treatment cannot be delayed for more than 2 weeks. • If ANC recovers to $>1000/\mu L$ by Day 14 of the scheduled date for the next cycle, administer full dose of study treatment.
Grade 3 or 4 thrombocytopenia on Day 1 of any Cycle, first episode	• Delay doses of all study treatment. • If platelet count recovers to $75,000/\mu L$ by Day 14 of the scheduled date of the next cycle, administer full dose of study treatment. • If the patient had baseline thrombocytopenia and the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of medications.
Recurrent Grade 3 or 4 thrombocytopenia	• Delay doses of all study treatment. • If platelet count recovers to $75,000/\mu L$ by Day 14 of the scheduled date of the next cycle, administer full dose of study treatment.
Grade 1 or 2 neutropenia and/or thrombocytopenia	• No dose reduction or delay
Grade 4 peripheral neuropathy (including its signs and symptoms)	• Discontinue polatuzumab vedotin permanently

Event(s)	Dose Delay or Modification

Grade 2 or 3 peripheral neuropathy (including its signs and symptoms)	• Delay all study treatment
	• If recovered to Grade ≤ 1 within ≤ 14 days of the scheduled date of the next cycle:
	  • If the dose of polatuzumab vedotin is 1.8 mg/kg, then reduce polatuzumab vedotin to 1.4 mg/kg (permanent dose reduction). RCHP may be administered at their full doses.
	  • If there was a prior dose reduction of polatuzumab vedotin to 1.4 mg/kg for Grade 2 or 3 neurotoxicity: all study treatment must be permanently discontinued.
	• If not recovered to Grade ≤ 1 until 14 days or after the scheduled date for the next cycle, Polatuzumab Vedotin must be permanently discontinued. Resumption of PV for future cycles may be considered upon discussion with the medical monitor.

Total Bilirubin > 3.0 mg/dL	• Delay treatment until resolution to ≤ 1.5 mg/dL within ≤ 14 days. Evaluate for causality. • Any case involving an increase in hepatic transaminase >3 × baseline AND an increase in direct bilirubin > 2 × ULN, WITHOUT any findings of cholestasis or jaundice or signs of hepatic dysfunction AND in the absence of other contributory factors (e.g., worsening of metastatic disease or concomitant exposure to known hepatotoxic agent or of a documented infectious etiology) is suggestive of potential treatment toxicity, and study treatment should be discontinued.
Grade 3 or 4 tumor lysis syndrome	• Hold all study treatment. The patient's next dose may be delayed for up to 14 days. • Begin appropriate TLS measures (IVF, rasburicase if needed, allopurinol, hospitalization) per institutional guidelines • Following complete resolution TLS, study treatment may be re-administered at the full dose during next scheduled infusion, in conjunction with prophylactic therapy.
Grade 3 or 4 non-hematologic toxicity not specifically described above (excluding alopecia, nausea, and vomiting)	• Delay study treatment for a maximum of 14 days • If improvement to Grade ≤ 1 or baseline, continue study therapy at full dose, or dose reduce at the discretion of the investigator per site's standard after discussion with the Medical Monitor.
Grade 2 non-hematologic toxicity	• Delay study treatment for a maximum of 14 days. • If improvement to Grade ≤ 1 or baseline, administer previous doses of study treatment.
Grade 1 non-hematologic toxicity	• No dose reduction or delay

Event(s)	Dose Delay or Modification
Hepatitis B reactivation (as noted by new detectable HBV-DNA levels)	• HBV-DNA levels between WHO-recommended range of 29 and 100 IU/mL: Re-test within 2 weeks. If still positive, hold all study treatment and treat patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist, ID specialist or hepatologist. • HBV-DNA levels at WHO-recommended cutoff of 100 IU/mL: hold all study treatment and treat the patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist, ID specialist or hepatologist. • Rising HBV-DNA viral load (exceeding 100 IU/mL) while on an appropriate anti-viral therapy: Discontinue all study treatment immediately.

ANC = absolute neutrophil count; DILI = drug-induced liver injury; G-CSF = granulocyte colony stimulating factor; HBV = hepatitis B virus; LMWH = low molecular-weight heparin; R = rituximab; ULN = upper limit of normal; WHO = World Health Organization.

[A] All based on laboratory test results obtained within 72 hours before infusion of Day 1 of that cycle.

[B] If the clinical condition of patient requires the use of concomitant anticoagulants, the patients are at increased risk of bleeding when thrombocytopenia with platelets < 20.000/µL develops. When possible, replace prior therapy with vitamin K antagonists with LMWH before Cycle 1 Day 1.

[C] Clinical decision making may be adjusted depending on the patient-specific assessment of benefit and risk.

5.1.4.4. Hematologic Toxicity

Note that lymphopenia is not considered to be a hematologic toxicity because it is an expected outcome of therapy. See Table 2 for specific guidance.

5.1.4.4.1. Dose Discontinuation

Dosing delay exceeding 14 days in the initiation of the next planned cycle polatuzumab vedotin plus R-CHP will require study treatment discontinuation unless Medical Monitor approval is obtained to continue on study treatment.

If scheduled dosing coincides with a holiday that precludes dosing, commence dosing on the nearest following date, with subsequent dosing continuing on a 21- or 28-day schedule as applicable.

Patients who discontinue all study treatment for adverse events should remain in the study and continue to have disease assessments until progression and standard follow up per Section 4.4.

5.1.4.5. Treatment Discontinuation Criteria

5.1.4.5.1. Polatuzumab Vedotin

A patient should permanently discontinue polatuzumab vedotin if any of the following occur:

- Grade 4 peripheral neuropathy
- Grade 3 peripheral neuropathy that leads to a treatment delay of 14 days or more and does not improve to Grade ≤ 1 within 14 days
- Recurrence of a Grade ≥ 2 peripheral neuropathy at the reduced dose

5.1.4.5.2. Rituximab

A patient should permanently discontinue rituximab if any of the following occur:

- Grade 4 infusion-related symptom or anaphylaxis. The patient should be withdrawn from study treatment immediately and supportive treatment given.
- Recurrence of Grade 3 infusion-related symptoms at re-challenge, regardless of timing (e.g., within same session or at the next session)
- If patient has Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence.

5.1.4.5.3. Polatuzumab Vedotin plus R-CHP

A patient should permanently discontinue polatuzumab vedotin + R-CHP if any of the following occur:

- Grade 3 or 4 hematologic toxicity that does not resolve to Grade ≤ 2 and delays treatment by > 14 days despite administration of growth factors and transfusion support
- Grade ≥ 2 non-hematologic toxicity that does not resolve to Grade ≤ 1 or baseline value and delays treatment by > 14 days

- Hepatitis B reactivation despite initiation of the appropriate anti-viral therapy
- Disease progression

5.2. ADVERSE EVENT REPORTING

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (Aes) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), 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 subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with Untreated Double and Triple Hit Lymphoma that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, Aes that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.

- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all Aes and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The reporting period begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All Aes and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to study drugs (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should assess the attribution of the event to study drugs by the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of study drugs, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to study drugs; and/or the AE abates or resolves upon discontinuation of study drugs or dose reduction and, if applicable, reappears upon re- challenge.

No

Evidence exists that the AE has an etiology other than the study drugs (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study drugs administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the

Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting Aes at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting Aes or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported 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, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical

condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

e. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0 Update current versions) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

f. Abnormal Laboratory Values:

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is 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 (e.g., potassium supplementation for hypokalemia)
- or a change in concomitant therapy
- Is clinically significant in the investigator’s judgment
- Note: For oncology trials, certain abnormal values may not qualify as adverse
- events.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

g. Pregnancy

If a female subject becomes pregnant while receiving polatuzumab or within *3 months* after the last dose of polatuzumab, or if the female partner of a male study subject becomes pregnant while the study subject is receiving polatuzumab or within *5 months* after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Additionally, if a female subject becomes pregnant while receiving rituximab or within 12 months after the last dose of rituximab, or if the female partner of a male study subject becomes pregnant while the study subject is receiving rituximab or within 160 days after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

h. Post-Study Adverse Events

For studies involving collection of follow up until progression free period the investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a

female subject (including pregnancy occurring in the partner of a male study subject) who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports

i. Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

j. Other Special Situation Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

k. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

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:
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), 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

The Polatuzumab Events of Special Interest Are:

- Tumor lysis syndrome of any grade (irrespective of causality)
- Second malignancies

The Rituximab Events of Special Interest Are: N/A

5.3. EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

Certain events require immediate reporting to allow the Sponsor to take appropriate measures and address potential new risks in a clinical trial. The investigator must report such events to Karmanos within 24 hours of awareness of the event. These events must also be reported to Genentech per the timelines described below.

These events will be reported on FDA Medwatch Form 3500A (https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm048334.pdf). Please see page 99 for instructions on completing the Medwatch Form.

The following is a list of events that the investigator must report within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Any death not due to progression of lymphoma, regardless of relationship to study drug
- Non-serious adverse events of special interest
- Pregnancies
- Accidental overdoses or medication errors

Investigators must also comply with local requirements for reporting serious adverse events to the local IRB/EC.

Each site is responsible for reporting these events to both Karmanos and Genentech via email or fax:

Report to Karmanos within 24 hours:

delucan@karmanos.org

modid@karmanos.org

Fax: 313-576-8368

Report to Genentech per the timelines in the table below:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

Emergency Medical Contacts
Medical Monitor Contact Information

Medical Monitor:

Dipenkumar Modi M.D.

Mobile Telephone No.: **313-576-8739**
OR
313-676-0320

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

• The event resolves

• The event stabilizes

• The event returns to baseline, if a baseline value/status is available

• The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

• It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

Exchange OF SINGLE CASE REPORTS

The investigator will be responsible for collecting all protocol-defined Adverse Events (Aes)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed MedWatch form should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should call via:
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Serious Adverse Drug Reactions (SADRs)	*15 calendar days of the awareness date*
Other SAEs	30 calendar days of the awareness date.
Special Situation Reports (Pregnancy) Special Situation Reports (Other)	30 calendar days of the awareness date. 30 calendar days of the awareness date.
Product Complaints	15 calendar days of the awareness date.
AESIs	15 calendar days of the awareness date.

- **SADRs**
  Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **AESIs**
  AESIs requiring expedited reporting (related or possibly related to Genentech product or where the causality is assessed as unknown or not provided) shall be forwarded to Roche within fifteen (15) calendar days of the awareness date. Others (non-related to Roche product) shall be sent within thirty (30) calendar days.

- **Special Situation Reports**
  Pregnancy reports
  While such reports are not serious Aes or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

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 (see section 5.2.f for pregnancy reporting timelines). A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

- **Other Special Situation Reports,** as defined above, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.
- **Product Complaints**

  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via the investigator emailing Genentech a Quarterly line-listing documenting single case reports sent by the investigator to Genentech in the preceding time period.
The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by the investigator to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at
https://www.fda.gov/media/69876/download

Reporting to Regulatory Authorities, Ethics Committees and Investigators

The investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

The investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

The investigator, will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

The investigator, will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations. Safety information that occurs on other clinical studies utilizing polatuzumab vedotin will be distributed by Karmanos Cancer Institute directly to sites participating on this clinical study. Each site is responsible for reviewing and processing the safety reports per their policies.

AGGREGATE REPORTS

IND ANNUAL REPORTS

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech.

Copies of such reports should be mailed to the assigned Clinical Operations contact for the study at: polatuzumab-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by the investigator. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between all involved parties including sponsor and treating site. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. The investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Polatuzumab Vedotin (PoV) independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis

management issues relating to the Product. The investigator agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines. Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.
In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.
Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

5.4. EXPEDITED REPORTING TO REGULATORY AGENCIES

Serious adverse events that are unexpected and at least possibly related to the study drug will be reported to the FDA in an expedited manner by the IND holder (Karmanos Cancer Institute) according to 21 CFR 312.32.

It is the responsibility of the Investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, the sponsor's guidelines, and the Institutional Review Board policy.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The Phase II study is designed to assess the safety and tolerability of the combination of polatuzumab vedotin with R-CHP in Double or triple hit lymphoma subtypes of DLBCL.

6.1. DETERMINATION OF SAMPLE SIZE

The sample size is justified using Simon's two-stage optimal design. The null hypothesis that the true complete remission (CR) rate is 20% will be tested against the alternative CR rate of 35%. In the first stage, 13 patients will be accrued. If there are 2 or fewer

responses in these 13 patients, the study will be stopped. Otherwise, 33 additional patients will be accrued for a total of 46. The null hypothesis will be rejected if 13 or more responses are observed in 46 patients. This design yields a 1-sided type I error rate of 10% and power of 80% when the true response rate is 35%. Considering the drop-out rate (including nonevaluable patients) of 5%, the required sample size would be 49 patients. We allowed a high false positive rate because the DLBCL (diffuse large B-cell lymphoma), which is an inclusion criterion, is a rare disease and there is an urgent need for novel therapeutic strategies in this high-risk study population.

The expected accrual rate is 2 patients per month on the basis of a total of four institutions. The first stage patients (i.e., 13 patients) will be accrued at KCI and another institution (i.e., two institutions) and 33 additional patients will be accrued at all four institutions. Thus, it will take about 31 months (= 13 months + 18 months) to enroll 49 patients. Taking into account additional 6 months to be approved by all four institutional IRBs, it will take about 37 months to enroll a total of 49 patients at all four institutions.

6.2. SUMMARY OF CONDUCT OF STUDY

The analysis populations are as follows:

- All treated subjects: patients who receive at least one study treatment
- All response evaluable subjects: all treated subjects who have evaluable tumor measurement
- Biomarker subjects: all treated subjects with available biomarker data.

Patient baseline and clinical characteristics will be descriptively summarized for all treated subjects. The efficacy and safety analyses will be performed based on all treated subjects. The exploratory analysis will be carried out based on the biomarker subjects. The primary efficacy analysis will be also performed based on all response evaluable subjects as a sensitivity analysis.

6.3. EFFICACY ANALYSES

The efficacy analysis will be performed based on all treated subjects.

6.3.1. Primary Efficacy Endpoint and Analysis

The complete remission (CR) rate is the primary efficacy endpoint. The CR will be determined using the Lugano Response Criteria (Cheson et al. 2014), specified in Appendix 3, at the time of primary response assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication). The CR rate will be summarized by a bionomial response rate and its associated 2-sided 80% confidence interval (CI) using Pearson-Klopper method. The primary efficacy analysis will be also performed based on all response evaluable subjects as a sensitivity analysis.

6.3.2. Secondary Efficacy Endpoints and Analyses

The progression-free survival (PFS) will be defined as the duration from the start date of the treatment until the date of progression or death from any cause, whichever occurs first and the overall survival (OS) will be defined as the duration from the start date of

the treatment until the date of death from any cause. The distributions of PFS and OS will be graphically summarized using the Kaplan-Meier (KM) curve and the median PFS/OS and their associated 2-sided Cis will be estimated using the KM estimator. The median follow-up times and their 2-sided Cis will be estimated using the reverse KM estimator.

The overall response rate (ORR) is defined as the proportion of patients who have CR or partial response (PR) at primary response assessment based on the Lugano Response Criteria specified in Appendix 3 among all treated subjects. CR and PR will be summarized using frequency and percentage. The ORR will be summarized by a bionomial response rate and its associated 2-sided confidence interval (CI) using Pearson-Klopper method.

The duration of response (DOR) will be measured from the date of CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is documented among all treated subjects who had a confirmed CR or PR. The distribution of DOR will be graphically summarized using the Kaplan-Meier (KM) curve and the median PFS and its associated 2-sided CI will be estimated using the KM estimator.

6.4. SAFETY ANALYSES

Safety will be assessed through summaries of adverse events, summaries of changes from screening assessments in laboratory test results, ECGs, and changes in vital signs.

All adverse events occurring on or after first study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTC Adverse Event v5.0 toxicity grade. All serious adverse events will be listed separately and summarized.

Deaths reported during the study treatment period and those reported during follow-up after treatment discontinuation will be listed.

Relevant laboratory and vital sign (temperature, heart rate, respiratory rate, and blood pressure) data will be displayed by time, with NCI CTCAE v5.0. Grade 3 and 4 values identified where appropriate.

6.5. EXPLORATORY ANALYSES

Exploratory analyses of biomarkers (see Section 3.5.3.) related to tumor biology and the mechanisms of action of polatuzumab vedotin and rituximab will be conducted. Analyses will assess prognostic and/or predictive value of candidate biomarkers separately for each histological subtype and both investigator and IRC assessed outcomes. Specifically, the association between candidate biomarkers and PET-CT CR rate and OR rate and potentially other measures of efficacy and safety, independent of treatment, will be explored to assess potential prognostic value. In addition, the potential effect modification of treatment effect on PET-CT CR rate and OR rate and

potentially other measures of efficacy and safety, by biomarker status, will be explored to assess potential predictive value.

6.6 INTERIM AND FINAL ANALYSES

One interim analysis of CR rate will be performed when the first 13 patients have been treated. If there are 2 or fewer CRs in these 13 patients, the study will be stopped. Otherwise, 33 additional subjects will be accrued for the second stage, resulting in a total of 46 treated subjects. The null hypothesis will be rejected if 13 or more CRs are observed in these 46 patients.

7. DATA COLLECTION AND MANAGEMENT

7.1. DATA AND SAFETY MONITORING

1. Scheduled meetings will be held monthly or more frequently depending on the activity of the protocol. These meetings will include the protocol investigators and research staff involved with the conduct of the protocol.

2. During these meetings the investigators will discuss:

- Safety of protocol participants (adverse events and reporting)
- Validity and integrity of the data (data completeness on case report forms and complete source documentation)
- Enrollment rate relative to expectation of target accrual, (eligible and ineligible
- participants)
- Retention of participants, adherence to the protocol and protocol deviations
- Protocol amendments

3. Completed Data and Safety Monitoring Reports of these regular investigator meetings will be kept on file in the Clinical Trials Office (see form in appendix 7). The study coordinator assigned to the clinical trial at each site will be responsible for completing the report form. The completed reports will be reviewed and signed off by the site Principal Investigator (PI) or by one of the Co-investigators in the absence of the PI. The study coordinator will submit the completed forms to the Data and Safety Monitoring Committee.

4. The Barbara Ann Karmanos Cancer Institute, Data and Safety Monitoring Committee (DSMC) provide the primary oversight of data and safety monitoring for KCI

Investigator-initiated trials. The DSMC will meet on a regular basis to review the prior Serious Adverse Event forms and Data and Safety Monitoring study specific reports that have been filed.

7.2. DATA QUALITY ASSURANCE

Clinical trial data will be captured in OnCore's (Clinical Trial Management System) electronic data capture system. Site personnel will be trained on the eCRF system by the Karmanos OnCore administrator. Trial data entered in Oncore will be verified by source documentation.

CRFs should be completed within 10 business days of the availability of clinical documentation of a study visit. Data clarification and queries should be completed within 7 working days of notification.

Each participating site will submit source documents to KCI's clinical trials office. A KCI CTO monitor specialist will remotely monitor essential clinical trial data. Frequency of monitoring will be based on accrual at a site but will occur at least once every 1 month if a patient has been enrolled.

If deemed necessary by the primary site or sponsor an audit team may review contracted site data and materials in an on-site review.

7.3. SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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 that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained until otherwise instructed by the sponsor.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, DSMC audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4. RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ICFs, laboratory test results, and medication inventory records, must be retained by the site for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to

another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The 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 requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC and archived in the site's study file.

8.3. CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, 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 national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.4. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient last visit [LPLV]).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1. STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, ICF, and documentation of IRB/EC and governmental approval.

9.2. PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities.

9.3. ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed the Karmanos Cancer Institute. Clinical trial data will be captured in OnCore's (Clinical Trial Management System) electronic data capture system.

9.4. Publication of Data and Protection of Trade Secrets

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results

9.5. PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by Karmanos and submitted to Roche for

review and approval prior to local IRB submission. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements. Protocol amendments will be distributed to participating institutions for submission to their local IRB only after it is approved by the IRB at Karmanos.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Advani RH, Chen H, Habermann TM, et al. Comparison of conventional prognostic indices in patients older than 60 years with diffuse large B-cell lymphoma treated with R CHOP in the US Intergroup Study (ECOG 4494, CALGB 9793): consideration of age greater than 70 years in an elderly prognostic index (E-IPI). Br J Haematol 2010;151:143–51.

Agresti A. Categorical data analysis. 2nd edition. New York:Wiley, 2002.

American Cancer Society. Cancer Facts & Figures. Atlanta: American Cancer Society, http://www.cancer.org/acs/groups/content/@nho/documents/document/acspc-024113.pdf. 2010.

Anderson K, Bates MP, Slaughenhoupt BL, et al. Expression of human B cell associated antigens on leukemias and lymphomas: a model of human B cell differentiation. Blood 1984;63:1424–33.

Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998;16:2780–95.

Bishop JF, Schimpff SC, Diggs, CH, et al, Infections during intensive chemotherapy for non-Hodgkin's lymphoma. Ann Intern Med. 1981;95:549–555.

Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon-alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. J Clin Oncol 1997;15:1110.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics1982;38:29–41.

Brown JR, O'Brien S, Kingsley CD, et al. Safety and efficacy of obinutuzumab (GA101) with fludarabine/cyclophosphamide (G-FC) or bendamustine (G-B) in the initial therapy of patients with chronic lymphocytic leukemia (CLL): results from the Phase 1b GALTON trial (GAO4779g). Blood 2013;122:Abstract 523.

Calabrese LH, Molloy ES, Huang D, et al. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum 2007;56:2116–28.

Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009;113:4384–8.

Cavaletti G, Frigeni B, Lanzani F, et al. The total neuropathy score as assessment tool for grading the course of chemotherapy-induced peripheral neurotoxicity: comparison with the National Cancer Institute-Common Toxicity Scale. J Peripher Nerv Syst 2007;12:210–5.

Cavaletti G, Jann S, Pace A, et al. Multi-center assessment of the total neuropathy score for chemotherapy-induced peripheral neurotoxicity. J Peripher Nerv Syst 2006;11:135–41.

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86.

Cheson BD, Wendtner C-M, Pieper A, et al. Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an International Consensus Panel. Clin Lymphoma Myeloma Leuk 2010;10:21–7.

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.

Clopper C; Pearson E S. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404–13.

Coiffier B, Feugier P, Mounier N, et al. Long-term results of the GELA study comparing R-CHOP and CHOP chemotherapy in older patients with diffuse large B-cell lymphoma show good survival in poor-risk patients (abstract). J Clin Oncol 2007;25:443s.

Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235–42.

Coiffier B, Osmanov EA, Hong X, et al. Bortezomib plus rituximab vs. rituximab alone in patients with relapsed, rituximab-naïve or rituximab-sensitive follicular lymphoma: a randomized Phase 3 trial. Lancet Oncol 2011;12:773–84.

Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040–5.

Coleman M, Martin P, Ruan J, et al. Prednisone, etoposide, procarbazine, an cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: low-dose metronomic, multidrug therapy. Cancer 2008;112:2228–32.

Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin Lymphoma: a phase ii study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835–42.

Crump M, Kuruvilla J, Couban S, et al. Gemcitabine, dexamethasone, cisplatin (GDP) comparedwith dexamethasone, cytarabine, cisplatin (DHAP) salvage chemotherapy prior to autologous stem cell transplantation for relapsed and refractory aggressive lymphomas: final result of the phase III NCIC CTG Study LY12. Hematol Oncol 2013;31:Abstract 085.

Dornan D, Bennett F, Chen Y, et al. Therapeutic potential of an anti CD79b antibody-drug conjugate, anti–CD79b vc MMAE, for the treatment of non-Hodgkin lymphoma. Blood 2009;114:2721–9.

Doronina SO, Toki BE, Torgov MY, et al. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat Biotechnol 2003;21:778–4.

Dreyling M. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20:119–20.

Dyer MJS, Grigg A, González M, et al. Obinutuzumab (GA101) in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or bendamustine in patients with previously untreated follicular lymphoma (FL): results of the phase Ib GAUDI study (BO21000). Blood 2012;120:abstract 3686.

Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 2009;27:4555–62.

Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117–26.

Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a Phase II multicenter, single-agent study. J Clin Oncol 2008;26:204–10.

Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the National LymphoCare Study. J Clin Oncol 2009;27:1202–8.

Friedberg JW. How I treat double-hit lymphoma. Blood. 2017;130(5):590-6.

Gallagher CJ, Gregory WM, Jones AE, et al. Follicular lymphoma: prognostic factors for response and survival. J Clin Oncol 1986;4:1470–80.

Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184–90.

Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101–10.

Goldberg SL, Angora AL, Alter RS, et al. Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 2002;99:1486–8.

Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006;24:3121–7.

Han TH, Gopal AK, Ramchandren R, et al. CYP3A-mediated drug-drug interaction potential and excretion of brentuximab vedotin, and antibody-drug conjugate, in patients with CD30-positive hematologic malignancies. J Clin Pharm 2013;53:866–77.

Herold M, Haas A, Srock S, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group hematology and oncology study. J Clin Oncol 2007;25:1986–92.

Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of German Low-Grade Lymphoma Study Group. Blood 2005;106:3725–32.

International Agency for Research on Cancer, GLOBOCAN (IARC). Section of cancer information [resource on the internet]. 2008 [cited 2010 Nov 8]. Available from: http://globocan.iarc.fr/factsheets/populations/factsheet.asp?unp=990.

Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30(28):3452-9.

Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: Results from a multicenter study. Cancer 2010;116:106–14.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

Lyman GH, Dale DC, Friedberg J et al. Incidence and predictors of low chemotherapy dose-intesnsity in agreesive non-Hodgkin’s lymphoma: a nationwide study. J Clin Oncol 2004:22:4302–11.

Martín A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica 2008;93:1829–36.

Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. Haematol 2013;98:1726–31.

Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579–6.

Mosteller RD. Simplified calculation of body surface area. N Engl J Med 1987;317:1098.

National Comprehensive Cancer Network®. Clinical practice guidelines in oncology (NCCN Guidelines®) non-Hodgkin's Lymphomas (Version 1.2014). Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Oki Y, Noorani M, Lin P, Davis RE, Neelapu SS, Ma L, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. Brit J of Haematol. 2014;166(6):891-901.

Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2013;21:2103–9.

Petrich AM, Gandhi M, Jovanovic B, Castillo JJ, Rajguru S, Yang DT, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood. 2014;124(15):2354-61.

Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105–16.

Polson AG, Calemine Fenaux J, Chan P, et al. Antibody drug conjugates for the treatment of non-Hodgkin's lymphoma: target and linker drug selection. Cancer Res 2009;69:2358–64.

Polson AG, Yu SF, Elkins K, et al. Antibody drug conjugates targeted to CD79 for the treatment of non Hodgkin lymphoma. Blood 2007;110:616–23.

Robertson MJ, Kahl BS, Vose JM, et al. Phase II study of enzastaurin, a protein kinase C beta inhibitor, in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2007;25:1741–6.

Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4473–9.

Rummel MJ, Al-Batran SE, Kim SZ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non Hodgkin's lymphoma. J Clin Oncol 2005;23:3383–9.

Rummel M, Kaiser U, Belser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent, and mantle cell lymphomas–Final results of the randomized Phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas Germany). Blood 2010; 116:Abstract 856.

Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA GOELAMS FL2000 study. Blood 2008;112:4824–31.

Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Controlled Clinical Trial 1996;17:343–6.

Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007;109:1857–61.

Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive Non-Hodgkin's Lymphoma. N Engl J Med 1993;329:987–94.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205.

Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258–64.

Sweetenham JW. Diffuse large B-cell lymphoma: risk stratification and management of relapsed disease. Hematology Am Soc Hematol Educ Program 2005;252–9.

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90

Thomas SK, Mendoza TR, Vichaya EG, et al. Validation of the chemotherapy-induced neuropathy scale. J Clin Oncol 2012;30:9140.

Tilly H, Vitolo U, Walewski J, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23:78–82.

Tilly H, Morschhauser F, Bartlett NL, Sharman J, Haioun C, Kolibaba KS, et al. Polatuzumab Vedotin Combined with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (R-CHP) for Patients with Previously Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Updated Results of a Phase Ib/II Study. Blood. 2016;128(22):1853-.

Trotman J, Fournier M, Lamy T, et al. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol 2011;19:3194–200.

Vacirca JL, Acs PI, Tabbara IA, et al. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol 2014;93:403–9.

Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952–7.

Wilson WH, sin-Ho J, Pitcher BN, Hsi ED, Friedberg J, Cheson B, et al. Phase III Randomized Study of R-CHOP Versus DA-EPOCH-R and Molecular Analysis of Untreated Diffuse Large B-Cell Lymphoma: CALGB/Alliance 50303. Blood. 2016;128(22):469-.

Zelenetz AD, Abramson JS, Advani RH, et al. NCCN clinical practice guidelines in oncology: non-Hodgkin lymphoma. J Natl Compr Canc Netw 2010;8:288–334.

Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International Prognostic Index remains a valid predictor of outcome for patients with aggressive CD20+B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:2373–80.

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study visits	**Screening phase**	**Treatment phase (1 cycle = 21 days)**						**Suspected progression**	**End of treatment**	**Follow up visit up to 5 years after last treatment[m]**
		Cycle 1		**Cycle 2**		**Cycles 3-6[n]**				
		Day 1(±2 days)	**Day 3**	**Day 1(±2 days)**	**Day 3**	**Day 1(± 2 days)**	**Day 3**			
Study visit windows	**-28 days**							**Any time**	**Within 30 days (± 5 days) of last treatment**	**Every 3 or 6 months (± 14 days)**
Procedures										
Informed consent	X									
Medical history	X	X		X		X		X	X	X
Confirmation of eligibility	X									
Tumor biopsy	X[d]							X[i]		
Concomitant medications	X	X		X		X			X	
Adverse events[a]		X		X		X			X	X
Height	X									
Physical exam, vital signs, weight, ECOG	X	X		X		X		X	X	X
Disease assessment:										
PET/CT Scan[e]	X[e]					X[e]		X	X[e]	
CT/MRI Scan[f]	X[f]					X[e]		X[f]	X[e]	X[f]
Bone marrow biopsy and aspirate[g]	X[g]								X[g]	
Disease-related symptoms[h]	X	X		X		X		X	X	X

Study visits	Screening phase	Treatment phase (1 cycle = 21 days)						Suspected progression	End of treatment	Follow up visit up to 5 years after last treatment[m]
		Cycle 1		Cycle 2		Cycles 3-6[n]				
		Day 1(±2 days)	Day 3	Day 1(±2 days)	Day 3	Day 1(± 2 days)	Day 3			
Study visit windows	**-28 days**							**Any time**	**Within 30 days (± 5 days) of last treatment**	**Every 3 or 6 months (± 14 days)**
Procedures										
Overall response assessment –tumor grid completion						X		X	X	X
IPI	X									
CBC with differential	X	X		X		X				X
Comprehensive metabolic panel[b]	X	X		X		X				X
pregnancy test[o]	X	X		X		X				
Creatinine clearance (Cockcroft-Gault)	X	X		X		X				X
Hepatitis serologies	X[c]			X[j]		X[j]				
HIV	X									
B2-microglobulin	X									
Hemoglobin A1C	X[k]					X[k]				
PT, PTT, INR	X									
LDH	X									
12-lead EKG	X									
Echocardiogram or MUGA	X									
Polatuzumab plus R-CHP		X		X		X				
Intrathecal Methotrexate 12 mg[l]		X		X		X				
Neupogen/Neulasta/ Udenyca			X		X		X			

a: AEs are reported from the time the patient receives study drug until 30 days following last treatment of the study drug. In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported as adverse events for the duration of the study treatment and during any protocol specified follow-up periods including post-progression follow-up for overall survival. Peripheral neuropathy should be assessed at screening, on day 1 of each treatment cycles, and at the treatment completion visit.

b: Comprehensive metabolic panel includes sodium, potassium, chloride, bicarbonate, BUN/urea, calcium, albumin, glucose, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, magnesium, phosphorus, and Uric Acid. Amylase should be performed at screening only. **NOTE:** participants with diabetes must have weekly chemistries including glucose during cycles 1-3

c: Hepatitis serologies to be performed at screening include Hepatitis B surface antibody (HBsAb), HBsAg (surface antigen) and HBcAb (core antibody). If HBcAb (core antibody) is positive the patient will need negative HBV-DNA by PCR to be eligible for study. Hepatitis C serology includes Hepatitis C antibody (HCV antibody)..

d: Archival tissue is preferred if sample quantity is sufficient. If insufficient, fresh tissue biopsy can be performed.

e: PET/CT performed at screening, interim analysis between cycle 3 D15 to cycle 4 D15 then 6-8 weeks after cycle 6 D1 or last dose of study treatment, whichever is applicable.

f: Diagnostic quality CT of thorax, abdomen and pelvis (and neck if clinically indicated) with contrast performed during screening, interim analysis between cycle

3 day 15 to cycle 4 day 15, at EOT and/or progression and every 6 months after completion of treatment for up to one year.

g: Bone marrow biopsy and/or aspirate is optional per investigator's decision at screening however if positive must be performed at CR.

h: Disease-related symptoms include weight loss, fatigue, fever, night sweats, pruritus abdominal pain/discomfort due to splenomegaly including early satiety, and anorexia.

i: Tumor and/or bone marrow biopsy will be performed per investigator's discretion at the time of disease progression. The tissue sample will be processed per local pathology only. No additional testing is required per study.

j: HBV DNA PCR should be performed on Day 1 of each cycle ONLY for patients with occult or prior HBV infection (defined as negative HBsAb and positive hepatitis B core antibody (HBcAb). HCV RNA by PCR should be performed on Day 1 of each cycle if HCV antibody is positive at screening.

k: Hemoglobin A1C (HBA1C) should be performed at screening and on Day 1 cycle 4.

l: Intrathecal methotrexate 12 mg will be given on either day 1, 2 or 3 of each cycle as CNS prophylaxis.

m. Follow up will occur at every 3 months during first 2 years, and then every 6 months during the next 3 years

n. Patients who received a cycle of R-CHOP prior to study enrollment will still receive 6 cycles of R-CHP plus Polatuzumab

o. For women of child bearing potential, a pregnancy test will be obtained up to 7 days prior to cycle 1 day 1 of treatment . On day 1 of each subsequent cycle a serum OR urine pregnancy test will be performed. See section 4.4.7.1 for guidance in the event of any positive pregnancy test.

Appendix 2
Revised Criteria for Response Assessment: Lugano Classification

Response should be determined on the basis of radiographic and clinical evidence of disease. For the Primary Response Assessment, an FDG-PET (^{18}F fluorodeoxyglucose positron emission tomography)/CT (computed tomography) scan will be performed 6–8 weeks after Cycle 6 Day 1 as assessed by IRC and by investigator. Assessment of the PET-CT scan should follow the criteria described by Cheson BD 2014 presented below.

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

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

Appendix 2
Revised Criteria for Response Assessment: Lugano Classification (cont.)

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.

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).

Appendix 2
Revised Criteria for Response Assessment: Lugano Classification (cont.)

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 5PS[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 2
Revised Criteria for Response Assessment: Lugano Classification (cont.)

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

Appendix 2
Revised Criteria for Response Assessment: Lugano Classification (cont.)

Response	Site	PET-CT-based Response	CT-based Response
Partial (cont.)	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
None 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 2
Revised Criteria for Response Assessment: Lugano Classification (cont.)

Response	Site	PET-CT–based Response	CT-based Response
Progressive Disease		**Progressive metabolic disease**	**Progressive disease (requires at least 1 of the following)**
	Individual target nodes/nodal lesions 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 2
Revised Criteria for Response Assessment: Lugano Classification (cont.)

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 undertreatment).

[b] 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 3
Recommendations for the Use of White Blood Cell Growth Factors

PRIMARY PROPHYLACTIC G-CSF ADMINISTRATION (FIRST AND SUBSEQUENT-CYCLE USE)

Primary prophylaxis with growth-colony stimulating factor (G-CSF) is required.

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 et al. 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205.

Appendix 4
Recommended 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 and masks for oxygen delivery
- Airway management devices per standard of care
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines
- Salbutamol (or albuterol or equivalent)
- Antihistamines (H1 and H2 blockers)
- 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
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible.
- Administer epinephrine first, followed by antihistamines, albuterol, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 5
Commonly Used CYP1A2 Inhibitors and Inducers (Drugs, Foods, Over the Counter Medications, and Supplements) (cont.)

CYP1A2 Inhibitors	
Amiodarone	Imipramine
Amitriptyline	Isoniazid
Amlodipine	Ketoconazole
Anastrozole	Lidocaine
Caffeine	Losartan
Cimetidine (Tagamet)	Erythromycin
Ciprofloxacin (Cipro)	Estrogens
Citalopram	Mexiletine
Clarithromycin	Mexiletine
Clotrimazole	Modafenil
Clozapine	Nifedipine
Diclofenac	Olanzapine
Diltiazem	Omeprazole
Echinacea	Ondansetron
Ethinyl Estradiol	Paroxetinee
Fluoroquinolones	Propafenone
Fluconazole	Propanolol
Fluvoxamine	Ranitidine
Gemfibrozil	Rofecoxib
Ginseng	Sertraline

CYP1A2 Inducers	
Barbiturates (e.g., Phenobarbital)	Rifampin (e.g., Rifadin)
	Smoking
Cruciferous vegetables (broccoli, cauliflower, arugula, brussel sprouts, cabbage, kale, chard, turnips, radishes, wasabi, bok choy, watercress, collard	
Char-grilled meat	Triamterene (Dyrenium)
Carbamazepine (e.g., Tegretol)	Zolmitriptan (Zomig)
Primidone	

Adapted from ctep.cancer.gov/protocolDevelopment/docs/cyp1a2.doc.

Appendix 6
International Prognostic Index (IPI) for DLBCL

Age >60			
Serum lactate dehydrogenase concentration above normal			
ECOG PS ≥ 2			
Ann Arbor Stage III or IV			
Number of extranodal disease sites >1			
One point is given for each of the above characteristics present in the patient, for a total score ranging from zero to five. When applied to the initial group of 2031 patients with aggressive NHL treated with anthracycline-based regimens that did NOT include rituximab, five-year overall survival (OS) and complete response (CR) rates according to score were as follows:			
Score	Risk group	5-year OS, percent	CR rate, percent
0 to 1	Low risk	73	87
2	Low intermediate	51	67
3	High intermediate	43	55
4 to 5	High	26	44

Appendix 7
Barbara Ann Karmanos Cancer Institute
Data and Safety Monitoring (DSM) Report

PROTOCOL #: _____ **REPORT DATE:** _____

PROTOCOL TITLE

ATTENDANCE		

PROTOCOL ACTIVITY SINCE LAST REPORT			
Accrual Goal:	Eligible:		Total number of AE's to date:
Accrual to Date:	Ineligible (provide reason):		
Accrual Since Last Monthly Report:			

SPECIFICALLY FOR PHASE I TRIAL &/OR DOSE ESCALATING TRIALS:	
DOSE LEVEL	ACCRUAL
1	
2	
3	

RECORD ALL GRADE 3, 4, AND 5 AE'S AND GROUP BY CTCAE CATEGORIES. RECORD THE DATE OF THE OCCURRENCE, ATTRIBUTION AND IF REPORTABLE TO THE IRB. SHADE THE ROWS OF THE AE'S THAT HAVE OCCURRED FOR THIS REPORT. ATTACH THE IRB REPORT FORM FOR THE REPORTABLE EVENTS THAT OCCURRED ON THIS REPORT.

Pt. ID#	Category and type of adverse reaction	Date of Occurrence	Grade[1]	Attribution[2]	Reportable to IRB (Y/N) Yes with date

1. Grade: 1-Mild, 2-Moderate, 3- Severe, 4-Life-threatening, or 5- Death.
2. Attribution: 1-unrelated, 2 - unlikely, 3 - possibly, 4 - probably, or 5 - definitely

OFF TREATMENT: Provide reason [progression, death, toxicity, completed therapy, etc].
PROTOCOL DEVIATIONS: Accidental or unintentional change from the protocol.
PROTOCOL AMENDMENTS:Include date submitted and approved by the IRB.

DSM Report
Protocol #
Report Date:

OTHER COMMENTS			
Investigator Signature/Date:		**Study Coordinator Signature/Date:**	

Revised: 5/29/14