DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

MEDI4736-NHL-001

A PHASE 1/2, OPEN LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY AND TOLERABILITY OF DURVALUMAB (ANTI-PD-L1 ANTIBODY) AS MONOTHERAPY AND IN COMBINATION THERAPY IN SUBJECTS WITH LYMPHOMA OR CHRONIC LYMPHOCYTIC LEUKEMIA

The "FUSION NHL-001" Study

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STATISTICAL ANALYSIS PLAN

A PHASE 1/2, OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY AND TOLERABILITY OF DURVALUMAB (ANTI-PD-L1 ANTIBODY) AS MONOTHERAPY AND IN COMBINATION THERAPY IN SUBJECTS WITH LYMPHOMA OR CHRONIC LYMPHOCYTIC LEUKEMIA

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PROTOCOL NUMBER:	MEDI4736-NHL-001
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Lead Clinical Reseat Signature Printed Name	
Lead Product Safety Physician Signature _____ Printed Name _____ Date _____	

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

AE	Adverse event
AESI	Adverse event of special interest
ALT/SGPT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST/SGOT	Aspartate transaminase
ATC	Anatomical Therapeutical Chemical
AUC	Area under the curve
BSA	Body surface area
CI	Confidence interval
CL/F	Clearance
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum plasma concentration of drug
CR	Complete response
CRF	Case report form
CRi	Complete response with incomplete marrow recovery
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CxDy	Cycle x Day y
DI	Dose intensity
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
EE	Efficacy evaluable

Table 1: Abbreviations and Specialist Terms (Continued)

EMA	European Medicines Agency
FDA	Food and Drug Administration
FL	Follicular lymphoma
fT3	Free triiodothyronine
fT4	Free thyroxine
GRT	Global range table
GSSC	Global Scientific Steering Committee
HL	Hodgkin lymphoma
ICF	Informed consent form
INR	International normalized ratio
IP	Investigational product
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWG	International Working Group
IRT	Interactive response technology
IV	Intravenous
K	Terminal elimination rate constant
LEN	Lenalidomide
LLN	Lower limit of normal
LLOQ	Low limit of quantification
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum-tolerated dose
MZL	Marginal zone lymphoma
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma

Table 1: Abbreviations and Specialist Terms (Continued)

nPR	Nodular partial response
NTD	Non tolerated dose
ORR	Overall response rate
OS	Overall survival
Pd	Pharmacodynamics
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetics
PR	Partial response
PRL	Partial response with lymphocytosis
PS	Performance status
PT	Preferred term
R/R	Relapsed/refractory
RDI	Relative dose intensity
RP2D	Recommended Phase 2 dose
SAP	Statistical analysis plan
SAS®	Statistical Analysis System
SD	Stable disease
SLL	Small lymphocytic lymphoma
SMQ	Standardized MedDRA query
SOC	System organ class
sPD-L1	Plasma concentration of soluble PD-L1
SPM	Second primary malignancy
SRC	Safety review committee

Table 1: Abbreviations and Specialist Terms (Continued)

$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
TSH	Thyroid-stimulating hormone
V_z/F	Volume of distribution
WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol MEDI4736-NHL-001 "A Phase 1/2, open label, multicenter study to assess the safety and tolerability of durvalumab (anti-PD-L1 antibody) as monotherapy and in combination therapy in subjects with lymphoma or chronic lymphocytic leukemia."

This analysis plan is based on the final protocol version dated 06 Nov 2015, protocol amendment No. 1 dated 04 May 2017 and protocol amendment No 2 dated 14 Dec 2017. It contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety outcomes.

These analyses include one primary analysis. No formal interim analysis is planned for this study. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock and any data analysis for the final analysis. This SAP also provides a description of the strategy, rationale, and statistical techniques to be used to achieve the objectives of the dose-finding and dose-confirmation parts of the study. Dose-confirmation part enrollment can be adjusted according to the stopping rules described in Table 3.

This SAP will be finalized and signed prior to the clinical database lock for the primary analysis. All statistical analyses detailed in this SAP will be conducted using Statistical Analysis System (SAS®) Version 9.1 or higher.

On 05 Sep 2017, a Partial Clinical Hold was placed on this study by the United States (US) Food and Drug Administration (FDA). The decision by the FDA was based on risks identified in other trials for an anti-PD-1 antibody, pembrolizumab, in patients with multiple myeloma in combination with immunomodulatory agents. Enrollment into Arm A (durvalumab plus lenalidomide with or without rituximab) was discontinued. Subjects already enrolled and treated in Arm A before the Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the investigator, could continue study treatment if reconsented.

3. STUDY OBJECTIVES

On 05 Sep 2017, a Partial Clinical Hold was placed on this study by the US FDA. The decision by the FDA was based on risks identified in other trials for an anti-PD-1 antibody, pembrolizumab, in patients with multiple myeloma in combination with immunomodulatory agents. Enrollment into Arm A (durvalumab plus lenalidomide with or without rituximab) was discontinued. Subjects already enrolled and treated in Arm A before the Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the investigator, could continue study treatment if reconsented.

The dose-finding study part was completed for Arms B and C only. The dose-confirmation cohort of Arm A nor any of the dose expansion cohorts will open for enrollment.

Therefore, dose-expansion objectives and analyses were removed from the SAP.

3.1. Primary Objective

Dose-finding part:

- To assess the safety and tolerability of durvalumab when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab to determine the recommended Phase 2 dose (RP2D) of each combination in subjects with lymphoma or chronic lymphocytic leukemia (CLL).

Dose-confirmation part:

- To assess the safety of durvalumab as monotherapy and when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab at the RP2D in subjects with lymphoma or CLL.

3.2. Secondary Objectives

Dose-finding and Confirmation parts:

- To make a preliminary assessment of antitumor activity of durvalumab as monotherapy and when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab in subjects with lymphoma or CLL.

All parts:

- To characterize the pharmacokinetics (PK) of durvalumab as monotherapy and when given in combination.
- To characterize the PK of lenalidomide and ibrutinib when given in combination with durvalumab.
- To determine the pharmacodynamic (Pd) effects of durvalumab as monotherapy.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a multicenter, open label, Phase 1/2 study assessing the safety, tolerability, PK, Pd, and preliminary efficacy of durvalumab as monotherapy and when given in combination in select subtypes of relapsed or refractory (R/R) lymphoma or R/R CLL. The study will consist of 2 parts: dose-finding and dose-confirmation. Four treatment arms will be investigated:

- Arm A: durvalumab and lenalidomide ± rituximab

  On 05 Sep 2017, a Partial Clinical Hold was placed on this study by the US FDA. The decision by the FDA was based on risks identified in other trials for an anti-PD-1 antibody, pembrolizumab, in patients with multiple myeloma in combination with immunomodulatory agents. Enrollment into Arm A (durvalumab plus lenalidomide with or without rituximab) was discontinued. Subjects already enrolled and treated in Arm A before the Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the investigator, could continue study treatment if reconsented.
- Arm B: durvalumab and ibrutinib
- Arm C: durvalumab and rituximab ± bendamustine
- Arm D: durvalumab (monotherapy)

The study will start with 3 dose-finding cohorts (Arms A, B, and C) and 1 dose-confirmation cohort (Arm D).

All treatment arms will open for enrollment at study start (Note: US sites will not be enrolling patients into Arm D until full assessment of response from the combination therapy arms and initial data from Arm D from non-US sites has been submitted to the FDA. Subjects who meet the eligibility criteria for more than 1 treatment arm will be allocated to an open treatment arm by the sponsor based on site/principal investigator (PI) indicated preference.

The dose-finding part of the study was completed for Arms B and C only. The dose-confirmation cohort of Arm A nor any of the dose expansion cohorts will open for enrollment.

Dose-finding

Preliminary RP2D will be established for each durvalumab combination treatment using a 3 + 3 design (Storer, 1989). Please refer to Figure 1 for the overall study design.

For Arms A and C, prior to enrolling subjects to receive all 3 drugs, the doublet combinations (ie. Arm A: durvalumab and lenalidomide and Arm C: durvalumab and rituximab) will be evaluated. Once the doublet combinations are deemed tolerable, the eventual triplet combinations will be tested. The durvalumab starting dose is fixed in each of these arms.

Initially 3 to 6 subjects will be evaluated in each dose-finding cohort; therefore, approximately 15 to 60 (dose-limiting toxicity [DLT] evaluable) subjects with B-cell non-Hodgkin's lymphoma

(NHL) or CLL are anticipated to be enrolled in the dose-finding part. Subjects with CLL/small lymphocytic lymphoma (SLL) will not be eligible for Arm A. The final number of subjects will depend on the number of dose levels tested and the number of DLTs observed within each cohort. The durvalumab monotherapy arm will not have a dose-finding cohort as the preliminary RP2D has been established, but it will need to be confirmed.

During the dose-finding part, the decision to evaluate the next higher dose level for a combination agent, an intermediate dose level, the need to add additional subjects within any dose cohort, or to declare a dose level as tolerable will be made by the safety review committee (SRC), based on their review of clinical and laboratory safety data for a given dose cohort.

The SRC will identify a preliminary RP2D for each treatment arm (except Arm D) based on an integrated assessment of the safety, available PK and Pd data, and preliminary efficacy information.

Dose-confirmation

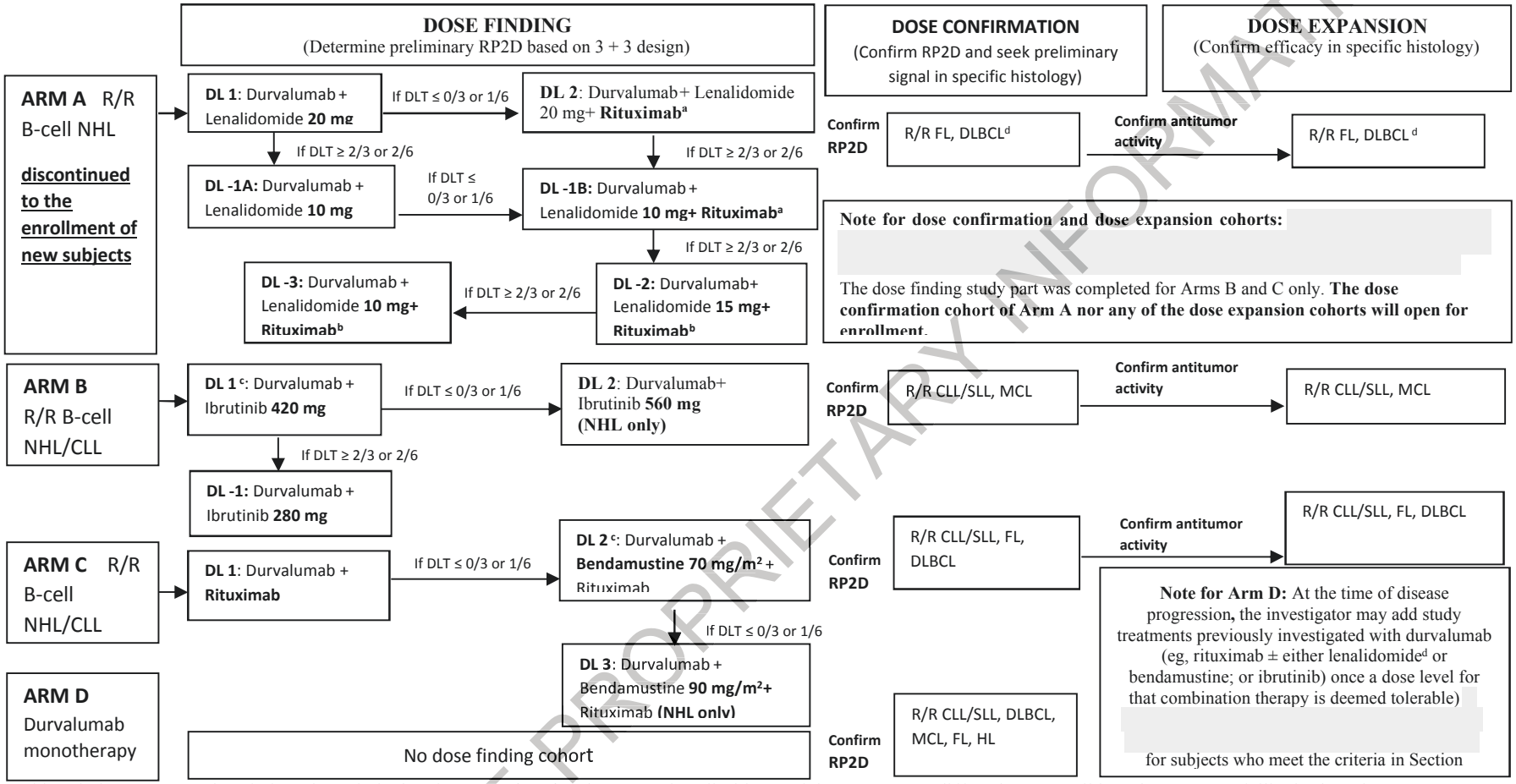
Once the preliminary RP2D is established, each combination treatment arm will enroll approximately 10 subjects with each of the prespecified disease histologies into Arms A, B, and C, to confirm the tolerability, and safety of the RP2D, and to identify the strongest antitumor signal in those histologies. The Arm D dose-confirmation cohort will be open at study start and enroll a total of approximately 30 subjects into up to 5 cohorts based on histology. In total, approximately 100 subjects are anticipated to enroll in the dose-confirmation part. The Arm D dose-confirmation part (durvalumab monotherapy) will start at the same time as the dose-finding part of the other 3 arms. Stopping rules as indicated in Table 3 have been predefined for each Arm/histology to allow for decision on further enrollment and to proceed to expansion phase.

All subjects will be evaluated for efficacy on a regular basis. The efficacy assessments for CLL will be based on the modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Response Criteria for CLL (Hallek, 2008; Hallek, 2012; Hallek, 2013) and for lymphoma based on the International Working Group (IWG) Response Criteria for Malignant Lymphoma (the Lugano Classification) (Cheson, 2014). The SRC will continue to review safety data regularly throughout the study for all cohorts in a treatment arm for late toxicities (which are clearly not related to disease progression or intercurrent illness) which may result in the need for dose reduction or discontinuation to make recommendations on dose modifications (eg. alternate schedule or dose levels) as appropriate. In addition, the SRC will review efficacy, PK or Pd data as available in order to make recommendations on, including, but not limited to, treatment cohort/study continuation and expansion in a specific disease histology. Each treatment arm has a dedicated SRC.

Based on the recommendations of the SRC and/or Global Scientific Steering Committee (GSSC), relevant emerging clinical or nonclinical data, the sponsor will decide whether or not to open any dose-confirmation as well as decide whether or not to adjust the number of subjects enrolled into any planned cohort.

Additional treatment arms and/or histologies may be added to the dose-confirmation part to explore the safety and efficacy as amendments to the protocol.

Figure 1: Overall Study Design



Abbreviations: CLL = chronic lymphocytic leukemia; DL = dose level; DLT = dose limiting toxicity; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin lymphoma; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; RP2D = recommended phase 2 dose; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma; SRC = safety review committee; US = United States.

[a] Arm A DL 2 and -1B **(discontinued to the enrollment of new subjects)**: Rituximab 375 mg/m^2 on Cycle 1 Days 2, 8, 15, 22 and then on Day 1 of every 28-day cycle from Cycles 2-5.

[b] Arm A DL -2 and -3 **(discontinued to the enrollment of new subjects)**: Rituximab 375 mg/m^2 on Cycle 1 Day 2 and then on Day 1 of every 28-day cycle from Cycles 2 through 8.

[c] Arm B DL 1 and Arm C DL 2: These dose levels will be the highest dose levels tested in subjects with CLL/SLL before opening CLL/SLL dose confirmation cohorts.

[d] Arm A dose confirmation and dose expansion cohorts are discontinued and will not enroll new subjects. In addition, the add-on combination treatment with lenalidomide ± rituximab is no longer allowed.

Notes: Durvalumab will be administered at a fixed dose of 1500 mg once every 4 weeks. All treatment arms will be open for enrollment at study start. Arm D will not be open for enrollment at the study start in the US, where Arm D will enroll depending on treatment slot availability and following the completion of an assessment of responses from the combination therapy arms (ie, Arms A, B, and C).

Study Population

Eligible subjects must have previously received treatment with at least 1 systemic therapy and currently have R/R lymphoma or CLL requiring therapeutic intervention. Subjects with lymphoma must have at least 1 measurable lesion by computed tomography (CT) scan (≥ 2 cm in the longest dimension). Subjects with CLL must be in need of treatment as defined by modified IWCLL Guidelines for the Diagnosis and Treatment of CLL (Hallek, 2008) Appendix I of the study protocol. All subjects must have adequate liver, renal, and bone marrow function as defined in Section 4 of the protocol.

Length of Study

The entire study is anticipated to last approximately 6 years and will consist of 3 periods: Screening, Treatment, and Follow-up.

During the Screening Period, lasting up to 28 days from the time of signing informed consent to Cycle 1 Day 1 (an exception may be biopsy samples), subjects will undergo assessments to determine their eligibility.

Subjects who qualify for enrollment into the study will enter the Treatment Period, during which subjects will receive investigational product(s) (IP[s]) at a predetermined dose and schedule for up to 13 cycles (in Arm A [only subjects with indolent NHL], Arm C, and Arm D); disease progression (in Arm A [subjects with aggressive NHL] and Arm B); or discontinuation of treatment due to unacceptable toxicity or other reasons. Please refer to section 9 of the protocol for further details.

Once subjects complete the Treatment Period, they will enter the Safety Follow-up Period. All subjects will be followed for adverse events (AEs) (including second primary malignancies [SPMs]) and concomitant medications/procedures for 90 days after the last dose of durvalumab or 28 days after the last dose of other IPs, whichever is the later date.

Subjects who have received lenalidomide (ie. subjects in Arm A or subjects in Arm D who have received lenalidomide as additional treatment at the time of progression) will be followed for SPMs for up to 5 years from the last subject's first lenalidomide dose.

In the Efficacy Follow-up Period, subjects will be followed for first progression, subsequent antilymphoma/CLL therapy, and overall survival (OS). In Arms A (indolent NHL: follicular lymphoma [FL] or marginal zone lymphoma [MZL]), C, and D, subjects will be followed for 24 months after their last durvalumab dose. In Arms A (aggressive NHL) and B, subjects will be followed for 24 months after their last durvalumab dose or their disease progression, whichever date occurs later.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary analysis, as prespecified in the protocol (whichever is the later date).

Study Treatments

Subjects will be assigned to 1 of the 4 treatment arms based on the investigator's choice led by the subject's eligibility status as per the inclusion/exclusion criteria described for each arm, prior antilymphoma/CLL therapy and response to prior therapy, medical history and also the availability of open treatment slots in a given cohort.

During each 28-day treatment cycle, subjects will receive durvalumab (intravenous [IV]) infusion on Day 1 of Cycles 1 through 13 at a fixed dose of 1500 mg every 4 weeks in combination with:

Treatment Arm A

- Lenalidomide orally (PO) once daily on Days 1 to 21 (inclusive) of each cycle for 12 months (Cycles 1 through 13) in indolent lymphoma histologies (eg. FL or MZL) or until disease progression in aggressive lymphoma histologies (eg. diffuse large B-cell lymphoma [DLBCL]) ± rituximab (IV) infusion:
    - Rituximab Schedule 1 (dose levels 2 or -1B): on Days 2, 8, 15 and 22 of Cycle 1 and on Day 1 of Cycles 2 through 5 or
    - Rituximab Schedule 2 (dose levels -2 and -3): on Day 2 of Cycle 1 and on Day 1 of Cycles 2 through 8 depending on the dose level assigned. Due to the study partial hold, the dose levels DL -2 and DL -3 will not be evaluated.

Note: Arm A is discontinued to the enrollment of new subjects at DL -1B (no enrollment in DL -2 and -3).Only subjects already enrolled and treated in Arm A who are receiving clinical benefit, based on the discretion of the investigator, may continue study treatment after being reconsented. In addition, the add-on combination treatment with lenalidomide ± rituximab is no longer allowed.

Treatment Arm B

- Ibrutinib (PO) continuous, once daily until disease progression.

Treatment Arm C

- Rituximab (IV) infusion on Day 2 of Cycles 1 through 6 ± bendamustine (IV) infusion on Days 1 and 2 of Cycles 1 through 6. Bendamustine may be stopped after 4 cycles if the subject experiences a cumulative toxicity related to bendamustine, and there is no clinical evidence of a favorable benefit to risk ratio for continuation of bendamustine treatment per the investigator's medical judgment.

Treatment Arm D

- Durvalumab monotherapy arm. At the time of disease progression, the investigator may add study treatments previously investigated with durvalumab in this protocol (ie. lenalidomide ± rituximab; bendamustine ± rituximab; rituximab; or ibrutinib) once a tolerable dose level is confirmed for that combination, f they meet the criteria defined in Section 3.1.2 of the study protocol. Prior to addition of another therapy to durvalumab, the investigator must consult with the sponsor's medical monitor.

4.2. Study Endpoints

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary Endpoints:			
Dose-finding	Safety	Nontolerated dose (NTD), maximum-tolerated dose (MTD), and recommended Phase 2 dose (RP2D) determined based on the incidence of dose limiting toxicities (DLTs) that occur during the DLT evaluation period	DLT evaluation period: from the first dose of any investigational product (IP) through the end of Cycle 1 when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab
		Incidence of treatment-emergent adverse events (TEAEs) using the NCI CTCAE criteria V4.03, including dose-limiting toxicities (DLTs)	From the first dose of any IP up to 90 days from the last dose of durvalumab or 28 days from the last dose of any other IP, whichever occurs later
Dose-confirmation	Safety	Incidence of treatment-emergent adverse events using the NCI CTCAE criteria V4.03	From the first dose of any IP up to 90 days from the last dose of durvalumab or 28 days from the last dose of any other IP, whichever occurs later
Dose-finding and confirmation	Preliminary antitumor activity: IWG Response Criteria for Malignant Lymphoma (the Lugano Classification) (Cheson, 2014)	ORR based on the tumor specific response criteria: ORR (lymphoma): Proportion of subjects with best response of PR or CR	During durvalumab treatment (up to 13 cycles)
Secondary Endpoints:			
	IWCLL Response Criteria for CLL (Hallek, 2008; Hallek, 2012; Hallek, 2013)	ORR (CLL): Proportion of subjects with best response of CR, CRi, nPR, PR, or PRL	

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
All parts	Other efficacy parameters: IWG Response Criteria for Malignant Lymphoma (the Lugano Classification) (Cheson, 2014) IWCLL Response Criteria for CLL (Hallek, 2008; Hallek, 2012; Hallek, 2013)	ORR based on the tumor specific response criteria: ORR (lymphoma): Proportion of subjects with best response of PR or CR ORR (CLL): Proportion of subjects with best response of CR, CRi, nPR, PR, or PRL	During the study treatment and the follow-up phase
	Duration of response (DoR)	DoR (lymphoma): Time from first CR or PR to progressive disease (PD) or death DoR (CLL): Time from first CR, CRi, nPR, PR, or PRL to PD or death	During the study treatment and the follow-up phase
	Time to response (TTR)	TTR (lymphoma): Time from first IP dose to first response (CR or PR) TTR (CLL): Time from IP dose to first response (CR, CRi, nPR, PR, or PRL)	During the study treatment and the follow-up phase
	Progression-free survival (PFS)	PFS (lymphoma/ CLL): Time from first IP dose to the first documented PD or death due to any cause, whichever occurs first	During the study treatment and the follow-up phase
All parts	PK	Serum/plasma samples will be collected to assay serum/plasma concentrations of durvalumab, lenalidomide and ibrutinib and to assess typical PK parameters such as maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), time to maximum concentration (T_{max}), terminal half-life ($t_{1/2}$), clearance (CL/F) and volume of distribution (V_z/F)	During Cycles 1 & 2

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Pd	Individual soluble PD-L1 (sPD-L1), soluble factors levels in blood at baseline and at specified time points (monotherapy)	During the study treatment

Abbreviations: CLL = chronic lymphocytic leukemia; IP = investigational product; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; IWG = International Working Group; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Pd = pharmacodynamic(s); PD-L1 = programmed cell death ligand 1; ; PK = pharmacokinetic(s).

4.3. Subject Allocation to Treatment Arms

The study will start with 3 dose-finding cohorts (Arms A, B, and C) and 1 dose-confirmation cohort (Arm D). All 4 treatment arms will be open for enrollment at study start.

An IRT will be used to track and make final subject assignments to the treatment arms and dose levels in all parts and arms of the study.

The cohort availability will be tracked centrally with a Cohort Management Tool which will show the most current cohort status and be available for site's view in the IRT website.

The treatment assignment in the dose-finding cohorts (ie. Arms A, B, and C) will be based on open dose levels, cohort availability, type of prior lymphoma/CLL therapy, and response to that therapy, and eligibility based on the inclusion/exclusion criteria.

The treatment assignment in the dose-confirmation and expansion cohorts will be based on cohort availability, type of prior lymphoma/CLL therapy, and response to that therapy, and eligibility based on the inclusion/exclusion criteria. For the planned number of patients with each histology in Arms A to D, refer to study protocol Table 3, Eligible Histologies per Treatment Arm and Part of the Study.

Investigators will be asked for their preference of treatment arm for each subject, and Sponsor will honor that request, whenever possible, according to cohort availability and study design.

4.4. Sample Size Determination

There is a maximum of 60 subjects required for the dose-finding part, a maximum of approximately 100 subjects for the dose-confirmation part, thus, a total of approximately 160 subjects for the entire study.

4.4.1. Dose-finding Part

There are 3 treatment arms in the dose-finding part, i.e. Arm A (discontinued to the enrollment of new subjects), Arm B, and Arm C. The standard "3 + 3" dose-escalation design will be used to identify the maximum tolerated dose (MTD) and RP2D for each treatment arm. The total sample size for the dose-finding part ranges from 15 to 60 subjects.

Subjects will be considered evaluable for DLTs if they complete the DLT evaluation period or experience a DLT during the DLT evaluation period. Non-evaluable subjects may be replaced with another subject at the same dose level.

Arm A (Discontinued to the enrollment of new subjects)

Subjects with R/R B-cell NHL will be enrolled into Arm A. There are 8 potential dose-finding paths:

- DL1 → DL2
- DL1 → DL2 → DL-1B

- DL1 → DL2 → DL-1B → DL-2
- DL1 → DL2 → DL-1B → DL-2 → DL-3
- DL1 → DL-1A
- DL1 → DL-1A → DL-1B
- DL1 → DL-1A → DL-1B → DL-2
- DL1 → DL-1A → DL-1B → DL-2 → DL-3

The sample size required for Arm A ranges from a minimum of 6 subjects (2 dose levels with 3 subjects per dose level) to a maximum of 30 subjects (5 dose levels with 6 subjects per dose level) as outlined in Figure 4 of the study protocol.

Arm B

Subjects with R/R B-cell NHL or CLL/SLL will be enrolled into Arm B. There are 2 potential dose-finding paths:

- DL1 → DL2 or
- DL1 → DL-1

The sample size required for Arm B ranges from a minimum of 6 subjects (2 dose levels with 3 subjects per dose level) to a maximum of 12 subjects (2 dose levels with 6 subjects per dose level) as outlined in Figure 5 of the study protocol.

Arm C

Subjects with R/R B-cell NHL or CLL/SLL will be enrolled into Arm C. There are 2 potential dose-finding paths:

- DL1 → DL2;
- DL1 → DL2 → DL3

The sample size required for Arm C ranges from a minimum of 3 subjects (1 dose level with 3 subjects per dose level) to a maximum of 18 subjects (3 dose levels with 6 subjects per dose level) as outlined in Figure 6 of the study protocol.

4.4.2. Dose-confirmation Part

In the dose-confirmation part, the planned sample size is based on clinical empirical and practical considerations traditionally used for Phase 1/2 studies.

For the dose confirmation, expected rate of overall response (CR/PR) was used in order to determine the stopping rule by targeting with 10 subjects a probability of less than 20% of observing response less or on the stopping rule (eg. for arm A, histology R/R, given expected ORR is 65%, probability of observing 4 or less responses out of 10 subjects is equal to ~9.5%, and probability of observing 5 or less responses out of 10 subjects is equal to ~24.9%).

Should the stopping rule described in Table 3 for the dose-confirmation part be fulfilled, the SRC for that cohort and GSSC will be consulted to determine whether the clinical trial should completely stop further enrollment of subjects with a particular histology (ie. not advance to the

dose-expansion part), temporarily halt enrollment and await maturation of efficacy data to examine for example durability of responses, or enroll additional subjects either in the dose-confirmation part or by formally advancing to the dose-expansion part. If there is no expected activity and/or stopping rules met for a certain dose level, other potential dose levels/schedules can be explored in the dose finding and confirmation parts based on the SRC and/or GSSC recommendation. The Sponsor may decide not to expand in any arm based on emerging internal or external data in relevant disease and therapeutic field or other reasons in consultation with the GSSC and/or SRC.

The total sample size for the dose-confirmation part is estimated to be approximately 100 subjects. The final number of subjects will depend on the number of subjects used to determine RP2D that can be determined in each arm/cohort in the dose-finding part.

Table 3: Stopping Rules for the Dose-confirmation Part for Efficacy

Treatment Arm	Subject Histology Cohort	Stopping Rule	Justification
A Discontinued to the enrollment of new subjects	R/R FL (N = 10)	≤ 4 overall responses	Based on literature that the rituximab-lenalidomide combination has ORR around 60%, the experimental arm has about 90% likelihood to continue the trial if its ORR is ≥ 65%.
	R/R DLBCL (N = 10)	≤ 2 overall responses	Based on literature that the rituximab-lenalidomide combination has ORR around 25-30%, the experimental arm has more than 80% likelihood to continue the trial if its ORR is ≥ 40%.
B	R/R CLL/SLL (N = 10)	≤ 5 overall responses	Based on literature that ibrutinib has ORR around 70% in the patient population being studied, the experimental arm has about 90% likelihood to continue the trial if its ORR is ≥ 75%.
	R/R MCL (N = 10)	≤ 5 overall responses	Based on literature that ibrutinib has ORR around 65%, the experimental arm has about 90% likelihood to continue the trial if its ORR is ≥ 75%.
C	R/R CLL/SLL (N = 10)	≤ 4 overall responses	Based on literature that rituximab + bendamustine combination has ORR around 50% in the patient population being studied, the experimental arm has about 90% likelihood to continue the trial if its ORR is ≥ 65%.
	R/R FL (N = 10)	≤ 2 CR	Based on literature that the standard care has CR rate around 40%, the experimental arm has about 90% likelihood to continue the trial if it's CR rate ≥ 45%.
	R/R DLBCL (N = 10)	≤ 2 overall responses	Based on literature that the standard care has ORR around 40%, the experimental arm has about 90% likelihood to continue the trial if its ORR is ≥ 45%.

Table 3: Stopping Rules for the Dose-confirmation Part for Efficacy (Continued)

Treatment Arm	Subject Histology Cohort	Stopping Rule	Justification
D	R/R CLL/SLL R/R DLBCL R/R FL R/R HL R/R MCL (5-10 subjects in each; total N = 30)		Information collection only.

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete response; FL = follicular lymphoma; DLBCL = diffuse large B-cell lymphoma; HL = Hodgkin's lymphoma; MCL = mantle cell lymphoma; N = number of subjects; ORR = overall response rate; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

- Data from all study centers will be combined for analysis;
- All statistical tests of the treatment effect will preserve a significance level of 0.050 for 2-sided tests. Testing of interactions will be performed at the 0.100 significance level;
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999';
- Confidence intervals will be presented as 2-sided 95% CIs unless specified differently in specific analysis;
- Summary statistics will consist of the number and percentage of subjects (or cycles, if appropriate) in each category for discrete variables, and the sample size, mean, median, standard deviation (SD), minimum, and maximum for continuous variables;
- All mean and median values will be formatted to 1 more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value;
- All percentages will be rounded to 1 decimal place. The number and percentage of responses will be presented in the form XX (XX.X%), where the percentage is in the parentheses;
- All listings will be sorted for presentation in order of treatment arm, study center, subject, and date of procedure or event;
- All analysis and summary tables will have the analysis population sample size (ie. number of subjects);
- The day of the first dose of any study drug will be defined as Day 1;
- Baseline value will be defined as the last value on or before the first dose of study drug is administered; if multiple values are present for the same date, the average of these values will be used as the baseline (for character parameters like urinalysis parameters, the worst value will be considered as baseline). For subjects who were not treated, the baseline will be the assessment value taken on the visit of Cycle 1 Day 1 if available; otherwise, the value on or prior to enrollment date will be used.

5.2. Analysis Population

5.2.1. Safety Population

The Safety Population (for all parts) is defined as all subjects who receive at least 1 dose of IP.

Drug exposure and all safety analyses (including AEs, laboratory values, and deaths) will be based on the Safety Population. Subjects will be analyzed according to the actual treatment arm and dose level initially received.

5.2.2. Efficacy Evaluable Population

Efficacy Evaluable (EE) Population (for the dose-finding, dose-confirmation, and dose-expansion part) is defined as all subjects who complete at least 1 cycle of their assigned treatment, have baseline, and at least 1 post-baseline tumor response assessment. Subjects will be analyzed according to their initial treatment arm and dose level allocation.

5.2.3. Dose-limiting Toxicity Evaluable Population

The DLT Evaluable Population (for the dose-finding part) is defined as all subjects in Arms A, B, and C, who take at least 1 dose of IP, and completed the DLT evaluation through the end of DLT evaluation period defined in the protocol, or the subjects who receive at least 1 dose of IP and have experienced at least 1 DLT prior to completion of the DLT evaluation period.

5.2.4. Pharmacokinetic Population

The PK Population is defined as all subjects who receive at least 1 dose of IP and have at least 1 measurable plasma concentration.

5.3. Definitions

5.3.1. Date of First Administration of Study Treatment

The date of first administration of study treatment is defined as the first date when a non-zero dose of any of the study drugs (durvalumab, lenalidomide, ibrutinib, bendamustine, or rituximab) was administered. This date will be collected in the case report form (CRF).

For simplicity, the date of first administration of study treatment will also be referred as the start date of study treatment.

5.3.2. Date of Last Administration of Study Treatment

The date of last administration of study treatment is defined as the last date when a non-zero dose of any of the study drugs (durvalumab, lenalidomide, ibrutinib, bendamustine, or rituximab) was administered. This date will be collected in the CRF.

5.3.3. Study Day

The study day for safety assessments (eg. AE onset, laboratory abnormality occurrence, vital sign measurement, and dose administration) will be calculated as the difference between the date of the assessment and the start date of study treatment plus 1.

The study day for time-to-event assessments (eg. time to response [TTR], duration of response [DOR], OS, or progression-free survival [PFS]) will be calculated as the difference between the date of the event and the date of treatment assignment plus 1.

The study day will be displayed in the data listings.

5.3.4. Baseline

The last available assessment before or on the date of start of study treatment is taken as "baseline" assessment.

5.3.5. Dose-limiting Toxicity

Dose-limiting toxicities will be evaluated during the DLT evaluation period for the subjects in the dose-finding cohorts.

Subjects will be evaluated for AEs at each visit with the NCI CTCAE Version 4.03 used as a guide for the grading of severity, with the exception of:

- Tumor lysis syndrome (Cairo, 2004) or
- Laboratory abnormalities in CLL subjects as recommended by the IWCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008) as listed in Appendix E of the study protocol.

5.3.6. Dose-limiting Toxicity Evaluation Period

Subjects enrolled in Arms A, B, and C will be observed for DLTs from the time of first IP dose through completion of the DLT evaluation period defined in the protocol.

5.3.7. Nontolerated Dose

A dose will be considered to be a nontolerated dose (NTD) if ≥ 2 of 3 or 6 evaluable subjects in a dose level experience a DLT.

5.3.8. Maximum Tolerated Dose

The MTD is defined as the highest dose level below the NTD with 0 of 3 or 1 of 6 (ie. < 1/3 of subjects) evaluable subjects experiencing DLTs during the DLT evaluation period.

5.3.9. Preliminary Recommended Phase 2 Dose

The SRC will identify a preliminary RP2D for each dose-finding cohort based on an integrated assessment of the safety, PK, Pd, and preliminary efficacy information. The RP2D selected will not exceed the MTD from the dose-finding cohorts.

The final number of subjects will depend on the number of dose levels and the number of DLTs observed within each cohort. The durvalumab monotherapy arm will not have a dose-finding cohort as the preliminary RP2D has been established, but it will need to be confirmed:

- In Arms A, B, and C, an initial cohort of 3 subjects will be enrolled to a specific dose level to assess toxicities, before additional subjects are treated in that arm.
- A dose level will be considered tolerable if 0 of 3 evaluable subjects experiences a DLT during the DLT evaluation period.
- If 1 of 3 subjects experiences a DLT, up to 3 more subjects will be enrolled at that dose level.
- A dose will be considered tolerable if ≤ 1 of 6 evaluable subjects experiences a DLT during the DLT evaluation period.
- A dose will be considered to be a nontolerated dose (NTD) if ≥ 2 of 3 or 6 evaluable subjects at a dose level experience a DLT.
- The MTD is defined as the highest dose level below the NTD with 0 of 3 or ≤ 1 of 6 evaluable subjects experiencing a DLT during DLT evaluation period.
- Subjects will be considered evaluable for DLTs if they complete the DLT evaluation period or experience a DLT during the DLT evaluation period. Nonevaluable subjects may be replaced with another subject at the same dose level.

6. SUBJECT DISPOSITION

The total number of subjects who fail screening ("screen failures") will be summarized with reason for screening failure.

A summary of subject disposition (subjects with ongoing assigned treatment, subjects completed with assigned treatment, subjects discontinued, along with primary reason for IP and study discontinuations) will be presented for the Safety Population and will be summarized using frequencies for Treatment and Follow-up Periods.

Reasons for **discontinued study treatment** will be summarized for all subjects with the following categories:

- Death
- Adverse event
- Progressive disease
- Lack of efficacy
- Withdrawal by subject
- Lost to follow-up
- Protocol violation
- Pregnancy
- Other.

Reasons for **discontinuing the study** (ie, no more follow up visit and no longer participating the study) will be collected on the CRF, and will be summarized for all enrolled subjects with the following categories:

- Death
- Adverse event
- Withdrawal by subject
- Lost to follow-up
- Other.

Listings will be provided for subjects enrolled but not treated with reasons, and for discontinued subjects with reason for treatment discontinuation.

The following by-subject listing of subjects will be provided:

- Subject listing of discontinuation
- Subject listing of screen failures.
- Subject listing of being excluded from Safety, DLT, EE, or PK Population.

7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations will be identified and assessed by clinical research physician or designee following company standard operational procedure. The protocol deviations/violations will be summarized by dose cohort and arm for the Safety Population.

A protocol violation/deviation is defined as any departure from the approved protocol that:

- Impacts the safety, rights, and/or welfare of the subject;
- Negatively impacts the quality or completeness of the data; or
- Makes the informed consent document/form inaccurate.

Protocol violations/deviations will be reported and monitored throughout the study. Data of protocol violations/deviations will be finalized prior to database lock.

A by-subject listing of subjects with protocol violations in the Safety Population will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized for the Safety Population. Individual subject listings will be provided to support the summary tables.

Summaries using descriptive statistics for the demographics and baseline characteristics will be carried out by particular treatment arm, histology, and study part.

8.1. Demographic and Baseline Characteristics

Age, height, weight, body surface area (BSA) based on Dubois' method, absolute neutrophils, platelets, alanine transaminase (ALT/SGPT), aspartate transaminase (AST/SGOT), total bilirubin, creatinine clearance, international normalized ratio (INR), activated partial thromboplastin time (aPTT), amylase, lipase, thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) will be summarized descriptively.

Age group (< 65 or ≥ 65, < 75 or ≥ 75 years), sex, childbearing potential, race, ethnicity, Eastern Co-operative Oncology Group (ECOG) performance status, and baseline ECG will be summarized by frequency counts.

8.2. Disease Characteristics at Baseline

Disease characteristics at baseline such as time from diagnosis, number of prior systemic regimens and time from end of last systemic regimen (see Section 16.2.4) will be summarized using descriptive statistics.

Categorical/ordinal variables such as best response to first systemic regimen, best response to last systemic regimen, best response to any prior systemic regimen, prior autologous transplantation, best response to prior autologous transplantation, stage of disease at baseline (Ann Arbor), bone marrow involvement at baseline, presence of B-symptoms at baseline, and presence of bulky disease at baseline will be summarized with frequency counts and percentages. Some other characteristics can be also summarized depending on the subject histology.

8.3. Medical History

A summary of medical history will be presented by Medical Dictionary for Regulatory Activities (MedDRA, Version 18 or higher) system organ class (SOC) and preferred term (PT).

8.4. Prior Anticancer Therapies

Whether subject had prior radiation therapy, prior cancer surgery, prior systemic anticancer therapy or prior stem cell transplantation will be summarized with frequency counts and percentages. In addition, prior exposure to anticancer therapies will also be summarized by regimen name with frequency counts and percentages.

8.5. Prior and Concomitant Medications

8.5.1. Prior Medications

Prior medications are defined as medications that were started before the start of the study treatment and either ended before the start of the study treatment or continued after study treatment.

A summary showing the number and percentage of subjects who took at least one prior medication will be presented by the World Health Organization (WHO) anatomical therapeutic class (ATC) and preferred drug name for the Safety Population.

8.5.2. Concomitant Medications

Concomitant medications are defined as medications that were either initiated before the first dose of study drug and continued during the study treatment, or initiated on/after the date of the first dose of study drug and on/before the date of treatment discontinuation (ie. until 90 days after the last dose of durvalumab or 28 days after the last dose of other IPs, whichever is the later date).

A summary showing the number and percentage of subjects who took at least one concomitant medications will be presented by the WHO ATC and preferred drug name for the Safety Population.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided based on the Safety Population. Descriptive statistics will be provided for treatment duration, number of cycles, cumulative dose, dose intensity (DI), and relative dose intensity (RDI) by treatment arm, histology, and dose level.

9.1. Treatment Duration

In this study the planned treatment duration of each drug is different, and therefore, the treatment duration of each drug will be summarized separately within the same treatment arm, histology, and dose level.

Treatment duration (weeks) for each drug (durvalumab, lenalidomide, ibrutinib, bendamustine, and rituximab) is defined as:

[(Treatment duration end date for individual study drug) – (date of Cycle 1 Day 1) + 1]/7

Treatment duration end date is defined as: Min [Max (last non-zero/non-missing dose date + days to be covered by the last dose), death date].

The number of days to be covered by the last dose is defined in Table 4.

Table 4: Number of Days to be Covered by the Last Dose

Arm	Schedule	n = days to be covered by the actual last dose
Arm A		
Durvalumab	CxD1	n = 27
Lenalidomide	CxD1 to CxD20 CxD21	n = 0 n = 7
Rituximab Dose level -1B, 2	C1D2 C1D8 C1D15 C1D22 CxD1	n = 5 n = 6 n = 6 n = 6 n = 27
Rituximab Dose level -2, -3	C1D2 CxD1	n = 26 n = 27
Arm B		
Durvalumab	CxD1	n = 27
Ibrutinib	CxD1 to CxD28	n = 0
Arm C		
Durvalumab	CxD1	n = 27
Bendamustine	CxD1 CxD2	n = 0 n = 26
Rituximab	CxD2	n = 26
Arm D		
Durvalumab	CxD1	n = 27
For other drugs, refer to above cases		

Abbreviation: CxDy = Cycle x Day y.

9.2. Cumulative Dose

The cumulative dose during treatment is defined as the sum of all doses taken across the treatment period for each study drug: durvalumab (in mg), lenalidomide (in mg), ibrutinib (in mg), rituximab (in mg/m^2), or bendamustine (in mg/m^2). Cumulative dose will be calculated separately for each drug by dose cohort, histology and treatment arm.

The number of subjects with overdoses will be also summarized separately for each drug by dose cohort, histology and treatment arm.

9.3. Dose Exposure

Dose exposure is defined as the total number of days for each drug separately during the treatment phase (excluding the periods of dose break per protocol or dose interruptions). Dose exposure will be calculated separately for each drug by dose cohort, histology, and treatment arm.

9.4. Average Daily Dose

Average daily dose of a particular drug is defined as the cumulative dose divided by dose exposure and expressed as mg/day or [mg/m^2]/day. Average dose will be calculated separately for each drug by dose cohort, histology, and treatment arm.

9.5. Dose Intensity

Dose intensity (DI) of a particular drug is defined as the cumulative dose per cycle and expressed as mg/cycle or [mg/m^2]/cycle. It is calculated as cumulative dose divided by the number of cycles of the drug. The number of cycles of the drug is determined as the last cycle during which a subject received the drug regardless of the cycle being completed or discontinued.

Dose intensity will be calculated for each drug separately by dose cohort, histology, and treatment arm.

Since in Arm A, dose level −1B and dose level 2, the rituximab dosing schedule is different for Cycle 1 and Cycles 2 to 5, its DI will be summarized for Cycle 1 and Cycles 2 through 5 separately.

9.6. Relative Dose Intensity

Relative dose intensity (RDI) is defined as the DI divided by the planned dose intensity* 100;

- For **durvalumab**, the planned DI is 1500 mg/cycle.
- For **lenalidomide** (Arm A), the planned DI is (lenalidomide RP2D*21)/cycle. The lenalidomide RP2D level can be 10 or 20 mg.
- For **rituximab** (Arm A), the planned DI is:
    - Dose level −1B and dose level 2:
        - [1500 mg/m^2]/cycle for Cycle 1 with dose level calculated based on subject's BSA.
        - [375 mg/m^2]/cycle for Cycle 2 through 5 with dose level calculated based on subject's BSA.
    - Dose level −2 and dose level −3: [375 mg/m^2]/cycle for Cycle 1 through 8 with dose level calculated based on subject's BSA.
- For **ibrutinib** (Arm B), the planned DI is (ibrutinib RP2D*28)/cycle. The ibrutinib RP2D level can be 280, 420, or 560 mg.

- For **rituximab** (Arm C), the planned DI is:
    - For subjects with CLL/SLL:
        - [375 mg/m^2]/cycle for Cycles 1 with dose level calculated based on subject's BSA.
        - [500 mg/m^2]/cycle for Cycles 2 through 6 with dose level calculated based on subject's BSA.
    - For all other subjects: [375 mg/m^2]/cycle for all cycles with dose level calculated based on subject's BSA.
- For **bendamustine** (Arm C), the planned DI is (bendamustine RP2D*2)/cycle for Cycles 1 through 6 with dose level calculated based on subject's BSA. The bendamustine RP2D level can be 70 or 90 mg/m^2.

Descriptive statistics of RDI will be presented for each drug separately, by dose cohort, histology, and treatment arm. RDI will not be displayed for dose finding part.

9.7. Dose Modification

Dose delay/reduction/interruption will be summarized separately for each drug. Summaries include subjects who had at least 1 dose delay/reduction/interruption, reason for the dose delay/reduction/interruption, and time to first dose delay/reduction/interruption.

Dose delay/reduction/interruption will be summarized for each drug separately, by dose cohort, histology, treatment arm and cycle.

There are 5 different actions which may be taken for each drug and captured in the CRF. All of these actions are not applicable to each drug (as summarized in the Table 5). The summary of actions taken will be customized for each drug (oral versus infusion).

Table 5: Actions Taken per Drug

	Dose delay	**Dose reduction**	**Dose interruption**	**Infusion interruption (complete or incomplete)**	**Drug withdrawn**
Durvalumab	X	n/a	n/a	X	X
Rituximab	X	n/a	n/a	X	X
Bendamustine	X	X	n/a	X	X
Ibrutinib	n/a	X	X	n/a	X
Lenalidomide	n/a	X	X	n/a	X

n/a = not applicable

10. EFFICACY ANALYSIS

All efficacy analyses will be carried out on the Safety or EE Populations. Efficacy analysis will be performed per arm, histology and study part by combining data from the dose-confirmation part. Efficacy analysis will also be performed separately for the dose-confirmation part and the dose-expansion part as well.

Final analyses will be performed after the End of Trial has been reached. All analyses will use descriptive statistics. All confidence intervals will be provided at a level of 95% confidence interval. No formal statistical comparison/testing will be performed.

For time-to-event endpoints (DoR and PFS) the detailed event and censoring criteria are listed in Table 6.

10.1. Response Rate

Overall response rate using the Lugano Classification

For lymphoma subjects, response evaluation will be based on IWG response criteria for malignant lymphoma (the Lugano Classification) (Cheson, 2014). ORR is defined as the percent of subjects with best response of CR or PR.

Overall response rate using the IWCLL Guidelines

For chronic lymphocytic leukemia subjects, response evaluation will be based on IWCLL guidelines for diagnosis and treatment of CLL. The ORR is defined as the percent of subjects with best response of CR, complete response with incomplete marrow recovery (CRi), nodular partial response (nPR), PR or partial response with lymphocytosis (PRL).

The ORR during durvalumab treatment (only for Arms A, B and C) as well as during entire efficacy evaluation period will be summarized by subject histology cohort for each treatment arm for both responses criteria (Lugano classification and IWCLL).

10.2. Time to Response

Time to response will be calculated as the time from first IP dose to the first response date (CR or PR for lymphoma subjects and CR, CRi, nPR, PR, or PRL for CLL subjects). TTR will be derived only for responder subjects.

TTR will be summarized using descriptive statistics (including only responder subjects) for each treatment arm.

10.3. Duration of Response

Duration of response using the Lugano Classification

Duration of response is defined for responders only as the time from the first documented response (CR or PR) to disease progression or death (from any cause). For subjects with response but no progression, or death, DoR will be censored at the last date that the subject was known to be progression-free.

Duration of response using the IWCLL Guidelines

Duration of response is defined for responders only as the time from the first documented response (CR, CRi, nPR, PR, or PRL) to disease progression or death (from any cause). For subjects with response but no progression, or death, DoR will be censored at the last date that the subject was known to be progression-free.

Duration of response will be assessed using the Kaplan-Meier method to calculate the median duration of response including 2-sided 95% CI for each treatment arm and subject histology cohort.

10.4. Progression-free Survival

Progression-free survival will be calculated as the time from first IP dose to the first documented progression or death (from any cause) during the entire efficacy evaluation period. For subjects with no progression or death, PFS will be censored at the last assessment date the subject was known to be progression-free. Median PFS including 2-sided 95% CI will be provided for each histology cohort within the same treatment arm.

The primary analysis will be based on the FDA guidelines (see Table 6 for the event and censoring rules). A sensitivity analysis will be performed using the European Medicines Agency (EMA) guidelines (see Table 7 for the event and censoring rules).

10.5. Overall Survival

Overall survival is calculated as the time from first IP dose to death due to any cause. Subjects who died will be considered as having events on the date of death. Subjects who were alive or lost to follow-up at the end of the study will be censored on the last-known-to-be-alive date. Overall survival will be analyzed similarly to PFS and DoR.

Table 6: Event and Censoring Rules for PFS and DoR Based on FDA Guidelines

Situation	Date Subject Has Event or is Censored	Situation Outcome
Progression not after 2 or more missed scheduled assessments during the treatment period	Date of PD	Event
Progression not after 1 or more missed scheduled assessments during the follow-up period	Date of PD	Event
Death not after 2 or more missed scheduled assessments during the treatment period	Date of death	Event
Death not after 1 or more missed scheduled assessments during the follow-up period	Date of death	Event

Table 6: Event and Censoring Rules for PFS and DoR Based on FDA Guidelines (Continued)

Situation	Date Subject Has Event or is Censored	Situation Outcome
Death or progression after 2 or more missed scheduled assessments during the treatment period	Date of last adequate assessment with evidence of no progression; if no adequate assessment exists then censored at date of first dose	Censored
Death or progression after 1 or more missed scheduled assessments during the follow-up period	Date of last adequate assessment with evidence of no progression; if no adequate assessment exists then censored at date of first dose	Censored
New anti-lymphoma/non-protocol treatment started prior to progression or death due to any reason. New anticancer therapy started prior to progression or death	Date of last adequate assessment with evidence of no progression before anticancer therapy; if no adequate assessment exists then censored at date of first dose	Censored
No progression	Date of last adequate assessment with evidence of no progression; if no adequate assessment exists then censored at date of first dose	Censored

Table 7: Event and Censoring Rules for PFS Based on EMA Guidelines

Situation	Date Subject Has Event or is Censored	Situation Outcome
Progression not after 2 or more missed scheduled assessments during the treatment period	Date of PD	Event
Progression not after 1 or more missed scheduled assessments during the follow-up period	Date of PD	Event
Death not after 2 or more missed scheduled assessments during the treatment period	Date of death	Event
Death not after 1 or more missed scheduled assessments during the follow-up period	Date of death	Event

Table 7: Event and Censoring Rules for PFS Based on EMA Guidelines (Continued)

Situation	Date Subject Has Event or is Censored	Situation Outcome
Death or progression after 2 or more missed scheduled assessments during the treatment period	Date of documented progression or death	Event
Death or progression after 1 or more missed scheduled assessments during the follow-up period	Date of documented progression or death	Event
New anti-lymphoma/non-protocol treatment started prior to progression or death due to any reason. New anticancer therapy started prior to progression or death	Date of documented progression or death	Event
No progression	Date of last adequate assessment with evidence of no progression; if no adequate assessment exists then censored at date of first dose	Censored

11. PHARMACOKINETIC ANALYSIS

Serum samples will be collected to assay the serum concentrations of durvalumab as monotherapy and in combination with other drugs, the plasma concentrations of lenalidomide in combination with durvalumab, and the plasma concentrations of ibrutinib in combination with durvalumab.

Serum/plasma concentrations from durvalumab and/or combo-drugs will be listed and summarized by cycle, day, nominal time, and cohort using descriptive statistics (N, mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum).

For concentration value below the low limit of quantification (LLOQ), a concentration value of zero will be included for the computation of arithmetic mean and a concentration value of 50% the LLOQ will be included for the computation of geometric mean.

Serum/plasma PK parameters (shown below but not limited to) will be calculated for durvalumab and/or combo-drugs using noncompartmental analysis:

- $AUC_{0\text{-last}}$: AUC from time 0 to the last measurable time point calculated using the log-linear trapezoidal method.
- $AUC_{0\text{-inf}}$: AUC from time 0 extrapolated to infinity, calculated as $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + lqc/K$, where lqc is the last quantifiable (measurable) concentration.
- C_{max}: Maximum (peak) concentration.
- T_{max}: Time of maximum (peak) concentration.
- K: Terminal elimination rate constant estimated by linear regression of log concentration vs. time; at least 3 data points are required to compute this parameter.
- $t_{1/2}$: Terminal elimination half-life computed as (log 2)/K.
- CL/F: Apparent systemic clearance, calculated as $Dose/AUC_{0\text{-inf}}$.
- V_Z/F: Apparent total volume of distribution, calculated as [CL/F/lz].

The log symbol above stands for natural log. PK parameters from durvalumab and/or combination IP will be listed and summarized by cycle, day, and cohort using descriptive statistics (N, mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum).

Mean and individual plots of plasma concentrations will be presented in both original and semilogarithmic scales.

12. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study. All summaries of safety data will be conducted using the Safety Population. All analyses will be presented by treatment arm, histology, study part, and dose level.

12.1. Dose-limiting Toxicity

Dose-limiting toxicities will be evaluated during the DLT evaluation period for the subjects in the dose-finding cohorts. The DLT evaluation period is starting from the first dose of any investigational product (IP) through the end of Cycle 1. The severity grading of adverse events will be determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher unless otherwise specify in protocol Section 7.2.10.1 (Cairo, 2004 and IWCLL, 2008).

Hematologic DLT:

- Grade 4 neutropenia observed for greater than 5 days duration;
- Grade 3 neutropenia associated with fever (≥ 38.5 °C) of any duration;
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion;
- Grade 4 anemia, unexplained by underlying disease;
- Any other grade 4 hematologic toxicity that does not resolve to subject's pre-treatment baseline level within 72 hours.

Nonhematologic DLT:

- Any nonhematological toxicity ≥ Grade 3 except for alopecia and nausea controlled by medical management;
- Any treatment interruption greater than 2 weeks due to adverse event.

While the rules for adjudicating DLTs in the context of dose-finding are specified above, an AE not listed above may be defined as a DLT after consultation with the sponsor and SRC based on the emerging safety profile.

Should a subject experience a suspected DLT, the treating investigator should contact the sponsor's medical monitor prior to declaring the event a DLT. All DLT cases will also be discussed with the SRC during regular calls with sites and their respective investigators aiming to review, and share all safety related events including but not limited to DLTs. Each study arm will have a dedicated SRC.

The number of subjects who experienced DLTs will be summarized using DLT Evaluable Population. Dose-limiting toxicities will be also listed by dose cohort and arm using the Safety Population.

12.2. Treatment-emergent Adverse Events

All safety analyses will be conducted using Safety Population. All analyses will be presented by treatment arm, histology, study part, and dose level. AEs will be coded according to the MedDRA Version 18 or higher.

Treatment-emergent adverse events (TEAEs) are defined as AEs occurring or worsening on or after the first treatment of the study treatment (durvalumab, lenalidomide, ibrutinib, bendamustine or rituximab) and within 90 days after last dose of durvalumab or 28 days after the last dose of other IPs, whichever is the later date, as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to study treatment.

The incidence of TEAEs will be summarized by MedDRA SOC and PT. The intensity of AEs will be graded according to the NCI CTCAE Version 4.03 or higher. For all other AEs not described in the CTCAE criteria, the intensity will be assessed by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or death (Grade 5).

A treatment-related TEAE is defined as TEAE which was considered to be related to the study drugs by the investigator.

If a subject experience the same AE more than once with different toxicity grade, then the event with the highest grade will be tabulated in "by grade" tables. If a subject experiences multiple AEs under the same PT (SOC), then the subject will be counted only once for that PT (SOC). In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of "Missing."

Tables summarizing the incidence of TEAEs will be generated per study phase within each arm for each of the following:

- All TEAEs;
- TEAEs related to durvalumab or any other IP;
- TEAE by CTCAE Grade 3 or 4;
- TEAE by CTCAE Grade 1 or 2;
- TEAE related to durvalumab or any other IP with Grade 3 or 4;
- TEAEs with death outcome;
- TEAEs with death outcome related to durvalumab or any other IP;
- Serious TEAEs;
- Serious TEAEs related to durvalumab or any other IP;
- TEAEs leading to discontinuation of durvalumab or any other IP;
- TEAEs leading to dose modifications of durvalumab or any other IP;
- TEAEs by cycle of onset;
- TEAEs related to durvalumab or any other IP by cycle onset;
- Serious TEAEs by cycle of onset;

- TEAEs by maximum CTCAE grade;
- TEAEs related to durvalumab or any other IP by maximum CTCAE grade;
- Common (≥ 10%) TEAEs;
- Common (≥ 10%) TEAEs related to durvalumab or any other IP.

To facilitate clinical study report writing, a summary table of TEAEs by PTs will also be provided.

Listings for the corresponding summary tables will be presented separately. A listing for non TEAEs will also be provided.

All deaths and reasons for death will be summarized. Deaths occurring during the treatment period, within 28 days after the last dose of durvalumab and within 90 days after the last dose of durvalumab will be summarized separately.

12.3. Adverse Events of Special Interest

The adverse events of special interest (AESI) refer to a group of terms/PTs from one or more SOCs relating to a defined medical condition or area of interest. Unless an AESI is defined by a single PT, the AESI generally refers to a group of PTs.

The AESI will be searched using the standardized MedDRA query (SMQ), sub-SMQ search criteria or a collection of selected ad-hoc PTs used to define and monitor the AESI. Adverse events of special interest will be summarized separately for durvalumab and lenalidomide. The AESI summary for each study treatment will be summarized by AESIs, which will be referred as AESI categories in tables and listings, and by PT.

Durvalumab AESI below will be summarized:

- Adrenal insufficiency
- Colitis
- Dermatitis
- Diarrhoea
- Guillain-Barre syndrome
- Hepatic laboratory parameters reported as AEs
- Hepatitis
- Hypersensitivity/Anaphylactic reactions
- Hyperthyroidism
- Hypophysitis
- Hypothyroidism
- Infusion related reaction
- Intestinal perforations

- Myasthenia gravis
- Myocarditis
- Myositis
- Nephritis
- Other rare/miscellaneous
- Pancreatic laboratory investigations reported as AEs
- Pancreatitis
- Pneumonitis
- Rash
- Renal laboratory investigations reported as AEs
- Thyroid laboratory parameters reported as AEs (decreased thyroid activity)
- Thyroid laboratory parameters reported as AEs (increased thyroid activity)
- Thyroiditis
- Type 1 diabetes mellitus.

Lenalidomide AESI below will also be summarized for subjects in Arms A and D who received lenalidomide:

- Cardiac arrhythmias
- Cardiac failure
- Infection
- Invasive-AML
- Invasive-B-cell malignancies
- Invasive-Cumulative
- Invasive-Other haematologic malignancies
- Invasive-Solid tumors-Cumulative
- Invasive-SPM hematologic malignancies
- Invasive-SPM solid tumor-Renal and urinary
- Invasive-SPM solid tumor-Reproductive
- Invasive-SPM solid tumor-Respiratory
- Invasive-SPM solid tumors-Breast
- Invasive-SPM solid tumors-Endocrine
- Invasive-SPM solid tumors-Gastrointestinal
- Invasive-SPM solid tumors-Hepatobiliary

- Invasive-SPM solid tumors-Skin
- Invasive-SPM solid tumors-Mesotheliomas
- Invasive-SPM solid tumors-Miscellaneous
- Invasive-SPM solid tumors-Nervous system
- Invasive-SPM solid tumors-Ocular
- Invasive-SPM solid tumors-Soft tissue
- Invasive-SPM solid tumors-Skeletal
- Ischaemic heart disease (including myocardial infarction)
- Neutropenia
- Non-invasive-SPM: Non-invasive skin cancers
- Teratogenicity
- Tumour flare reaction
- Unspecified.

The final list of AESI for durvalumab and lenalidomide will be defined before database lock.

The incidence will be generated by preferred term for:

- All TEAEs of interest;
- TEAEs of interest by CTCAE Grade 3 or 4;
- TEAEs of interest by cycle of onset;
- TEAEs of interest related to durvalumab or any other IP;
- TEAE of interest related to durvalumab or any other IP with Grade 3 or 4;
- TEAEs of interest by maximum CTCAE grade.

12.4. Second Primary Malignancies

Second primary malignancies will be collected at any time from the time of signing the informed consent form (ICF) until:

- 90 days after last dose of durvalumab;
- 28 days after last dose of other IPs; or
- Up to 5 years from last subjects' first lenalidomide dose for subjects in Arm A and subjects in Arm D who have received lenalidomide as additional treatment at the time of progression, whichever is the later date for an individual subject AESI.

The SPM events will be summarized by treatment arm, histology and study part. Summaries will present SPM as per categories, subcategories and preferred term. Graphical displays will be provided where useful to assist in the interpretation of results. Listings for the corresponding summary tables will be presented separately.

12.5. Clinical Laboratory Evaluations

Descriptive statistics (N, mean, standard deviation, median, minimum and maximum) of observed and change from baseline values will be presented for hematology and biochemistry laboratory tests.

Clinical laboratory values from the central laboratories will be graded according to NCI CTCAE Version 4.03 or higher for applicable tests. The worst grade during the treatment period will be summarized by treatment arm. Frequency distributions for shift from baseline to the worst grade during treatment period will be presented by treatment arm. Normal ranges will be used to determine the categories of High, Low, and Normal for all laboratory tests.

Listings of clinical laboratory data from central laboratory with abnormal flags will be provided by subjects and tests. Listings will also be provided for the local laboratory data. The local normal ranges data are derived based on global range table (GRT) file provided by Celgene.

12.7. Vital Sign Measurements

For vital signs, the shift from baseline to worst during the treatment in below, within, and above the normal ranges will be displayed in cross–tabulations for each treatment. Normal ranges are defined as follows:

- Systolic blood pressure (SBP) → Normal (100 – 140 mmHg, inclusive);
- Diastolic blood pressure (DBP) → Normal (60 – 90 mmHg, inclusive);
- Body temperature → Normal (35 – 38°C, inclusive);
- Pulse → Normal (60 – 100 bpm, inclusive).

Summary statistics (N, mean, standard deviation, median, minimum, and maximum) of the worst values of each cycle and change from baseline values will be presented.

The worst value at each cycle will be defined as follow:

- If all values during the cycle are within the normal range, the worst value will be the largest value;
- If one value during the cycle is outside the normal range, the worst value will be the value outside the normal range;
- If at least 2 values, during the cycle, are outside the normal range, the worst value will be the value having the largest absolute difference from the normal range bounds. In case of 2 values with same absolute difference, the largest value will be selected.

12.8. Overall Electrocardiograms Interpretation

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with 'Normal', 'Abnormal, not clinically significant', and 'Abnormal, clinically

significant' by treatment at Baseline. The shift from baseline to worst during the treatment in the overall ECG interpretation will be displayed in cross–tabulations for each treatment.

12.9. Eastern Co-operative Oncology Group Performance Scores

Shift table from baseline to worst post-baseline in ECOG performance score will be displayed by treatment arm and histology cohort for the Safety Population.

13. INTERIM ANALYSIS

No formal interim analyses are planned. However, the study will also have a GSSC providing advice to the sponsor regarding study protocol design/amendments, study conduct and scientific integrity of the study as well as providing guidance to each SRC as appropriate. The GSSC will serve in an advisory capacity to the sponsor.

Operational details for the SRC and GSSC will be detailed in a separate charter document.

The sponsor will decide whether or not to open any dose-confirmation or expansion cohort as well as decide whether or not to adjust the number of subjects enrolled into any planned cohort based on the recommendations of the SRC and/or GSSC and relevant emerging clinical or nonclinical data (the stopping rules for the dose-confirmation part are described in Table 3).

14. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

The dose-finding study part was completed for Arms B and C only. The dose-confirmation cohort of Arm A nor any of the dose expansion cohorts will open for enrollment.

15. REFERENCES

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16. APPENDICES

16.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie. the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as ongoing in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 17.2 (eg. for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (eg. the survival date is derived from the death date), or a procedure date (eg. the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

Dates recorded in comment fields will not be imputed or reported in any specific format.

16.1.1. Calculation Using Dates

Calculations using dates (eg. subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug (eg. lenalidomide) plus 1 day. The generalized calculation algorithm for relative day is the following:
  - If TARGET DATE >= DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
  - Else use STUDY DAY = TARGET DATE – DSTART.
- Note that Study Day 1 is the first day of treatment of study drug. Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.
- Age (expressed in days) is calculated: AGE = DATE of CONSENT – DATE of BIRTH + 1. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating. If date of birth is missing in the CRF then use the age recorded in the CRF.
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS/7
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS/30.4167
- Intervals that are presented in years will be transformed from days to years by using (without truncation) the following conversion formula:

  YEARS = DAYS/365.25

16.1.2. Calculation of Cycles

The start date of each treatment cycle will be calculated based on study drug exposure records for each subject. The start date of the first cycle will be the date when the subject receives any dose of study drug.

Once the start dates, eg. S_1, S_2, S_3… are calculated, the end date of each cycle is calculated as the day before the start date of the following cycle, ie. $E_i = S_{i+1} - 1$. For the last cycle, the end date will be calculated as the start date plus prescribed cycle length, or the treatment discontinuation date, or the death date, whichever is earlier. If a date is on or after S_i and before S_{i+1}, the corresponding cycle number will be i.

16.2. Date Imputation Guideline

16.2.1. Impute Missing Adverse Events/Prior or Concomitant Medications

Incomplete Start Date:

Missing day and month

- If the year is the same as the year of the first dosing date, then the day and month of the first doing date will be assigned to the missing fields.
- If the year is prior to the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is after the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the same as the year and month of first dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is before the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is before the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is after the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is after the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE.

Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is prior to the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is not equal to the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is not equal to the month of the last dosing date, then the last day of the month will be assigned to the missing day.

16.2.2. Medical History

Partially missing medical history start dates will be imputed in the ADaM dataset for medical history. The 16th of the month will be used to impute a partially missing start date that has only the day missing, and July 1st will be used to impute a partially missing start date that has both the month and day missing.

If the imputed start date is greater than the stop date:

- If the imputed start date is before the first treatment day then start date will be assigned to stop date.
- If the imputed start date is after the first treatment day then start date will be assigned to the first treatment day - 1.

16.2.3. Impute Missing Disease Diagnosis Dates

For partial diagnosis dates, January will be assigned to the missing month; and the first day of the month will be assigned to the missing day.

16.2.4. Impute Missing Dates in Prior Systemic Therapies

If day is missing, but month and year are non-missing:

- If start date has month strictly before month of end date, then impute day of end date to 1st of the month.
- If start date has month equal to month of end date and day of start day is missing, then impute day of end date to 1st of the month.
- If start date has month equal to month of end date and day of start day is non-missing, then impute day of the end date to the day of the start date.

If day and month are missing and year is non-missing:

- If start date has both day and month missing, then impute day to 1st of the month and month to January.
- If start date has day missing but month non-missing, then impute day to 1st of the month and month to the same month as start date.
- If start date has both day and month non-missing, then impute day and month to the same month to the day and month as the start date.

If day is non-missing, month is missing and year is non-missing:

- If start date has month missing, then impute month of the end date to January.
- If start date has month non-missing, then impute month of the end date to month of the start date.

If year is missing:

- No imputation.

16.2.5. Impute Missing Dates in Subsequent Cancer Therapy

Patient will allow take other cancer therapy after discontinued from the study. The lymphoma therapy start/stop date will be collected. If the day of any date is missing, then the last day the nonmissing month will be assigned to the missing day; if day and month are both missing, then the December 31 of the nonmissing year will be assigned to the missing day.

16.2.6. Impute Missing Dates for Death

If death day is missing, but month and year are non-missing:

- If patient discontinued the additional treatment period and the reason for discontinuation is death:
  - If month and year of the death date same as month and year of the discontinuation date then impute to date of additional treatment discontinuation date.
- If patient discontinued the follow-up period and the reason for discontinuation is death:
  - If month and year of the death date same as month and year of the discontinuation date then impute to date of follow-up discontinuation date.
- If patient discontinued the assigned treatment period and the reason for discontinuation is death:
  - If month and year of the death date same as month and year of the discontinuation date then impute to date of assigned treatment discontinuation date.
- If patient does not discontinue the assigned treatment period then impute to the last date patient known alive.

If death month or year is missing:

- No imputation.