Official Title of Study:

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

PROTOCOL(S) MEDI4736-NHL-001

NCT Number: NCT02733042

Document Date (Date in which document was last revised): April 22, 2020

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

PROTOCOL NUMBER:	**MEDI4736-NHL-001**
ORIGINAL DATE:	**06 Nov 2015**
AMENDMENT No. 1 DATE:	**04 May 2017**
AMENDMENT No. 2 DATE:	**14 Dec 2017**
AMENDMENT No. 3 DATE:	**12 Sep 2019**
AMENDMENT No. 4 DATE:	**22 April 2020**
EudraCT NUMBER:	**2015-003516-21**
IND NUMBER:	**127058**
SPONSOR NAME/ ADDRESS:	Celgene International II Sarl Rue des Moulins 4 2108 Couvet Switzerland

MEDICAL MONITORS / EMERGENCY CONTACT INFORMATION

Contact Information:
Name : [redacted]
Title: [redacted]
Address: Route de Perreux, Boudry, Switzerland
Phone: [redacted]
Mobile Phone: [redacted]
E-mail: [redacted]

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor(s) or designee for emergency calls.

Back-up 24-hour Global Emergency Contact Call Center: [redacted]

CELGENE THERAPEUTIC AREA HEADS SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:** _____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

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. As a result, enrollment into Arm A (durvalumab plus lenalidomide with or without rituximab) was discontinued. 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 December 2017, Celgene stopped enrollment and discontinued the dose expansion part of the study.

Following completion or discontinuation of durvalumab therapy per protocol for all subjects (n=106), and completion of the primary analysis (data cutoff date 06 Mar 2019, defined as last durvalumab subject's 90-day Safety Follow-up Visit), there are no further plans to evaluate long-term efficacy, including overall survival for the remaining subjects on study. Therefore, the Follow-up Period will be discontinued, and data collection will stop under this amendment. No additional statistical analysis on safety and efficacy will be performed.

At the time of primary analysis data cutoff, 36 subjects were in follow-up. There were 13 subjects on ibrutinib treatment (Arm B), and no subjects on treatment with lenalidomide or bendamustine. Subjects who continue ibrutinib on-study will be treated per investigator's medical judgement and standard of care at the investigative site or discontinue study to receive ibrutinib commercially as standard of care treatment (off-study).

Subjects who received lenalidomide will continue to be followed for second primary malignancies (SPMs) as required by [redacted] After stopping data collection in the clinical database, any SPM events will continue to be collected in the safety database.

Study Title

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 (MEDI4736-NHL-001). The "FUSION NHL-001" Study.

Indication

Relapsed/refractory (R/R) lymphoma or R/R chronic lymphocytic leukemia (CLL) previously treated with at least one systemic therapy.

Objectives

Arm A is discontinued to the enrollment of new subjects. Only those 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.

Primary:

Dose finding part (Phase 1):

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 doses (RP2Ds) of each combination.

Dose confirmation part (Phase 1):

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

Dose expansion part (Phase 2):

To evaluate the preliminary efficacy of durvalumab when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab in subjects with lymphoma or CLL

Secondary:

Dose finding and confirmation parts (Phase 1):

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

Dose expansion part (Phase 2):

To assess the safety of durvalumab when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab in subjects with lymphoma or CLL

All parts (Phase 1/2)

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

Exploratory:

To explore population PK analyses including the influence of intrinsic and extrinsic factors that may influence durvalumab exposures

To determine the immunogenicity of durvalumab as monotherapy and when given in combination

To explore PK/Pd relationship, explore pharmacodynamic mechanistic biomarkers for durvalumab and other combination agents in the study

To explore host immune and tumor molecular markers predictive of response to durvalumab and other agents when given in combination

To explore minimal residual disease (MRD) and its correlation with clinical outcome

To explore the abscopal effect (ie, immune-mediated tumor response outside the radiation field) of involved field radiation therapy when given in combination with durvalumab

Study Design

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

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 R/R lymphoma or R/R CLL.

The study will consist of 3 parts: dose finding, dose confirmation, and dose expansion. Four treatment arms will be investigated:

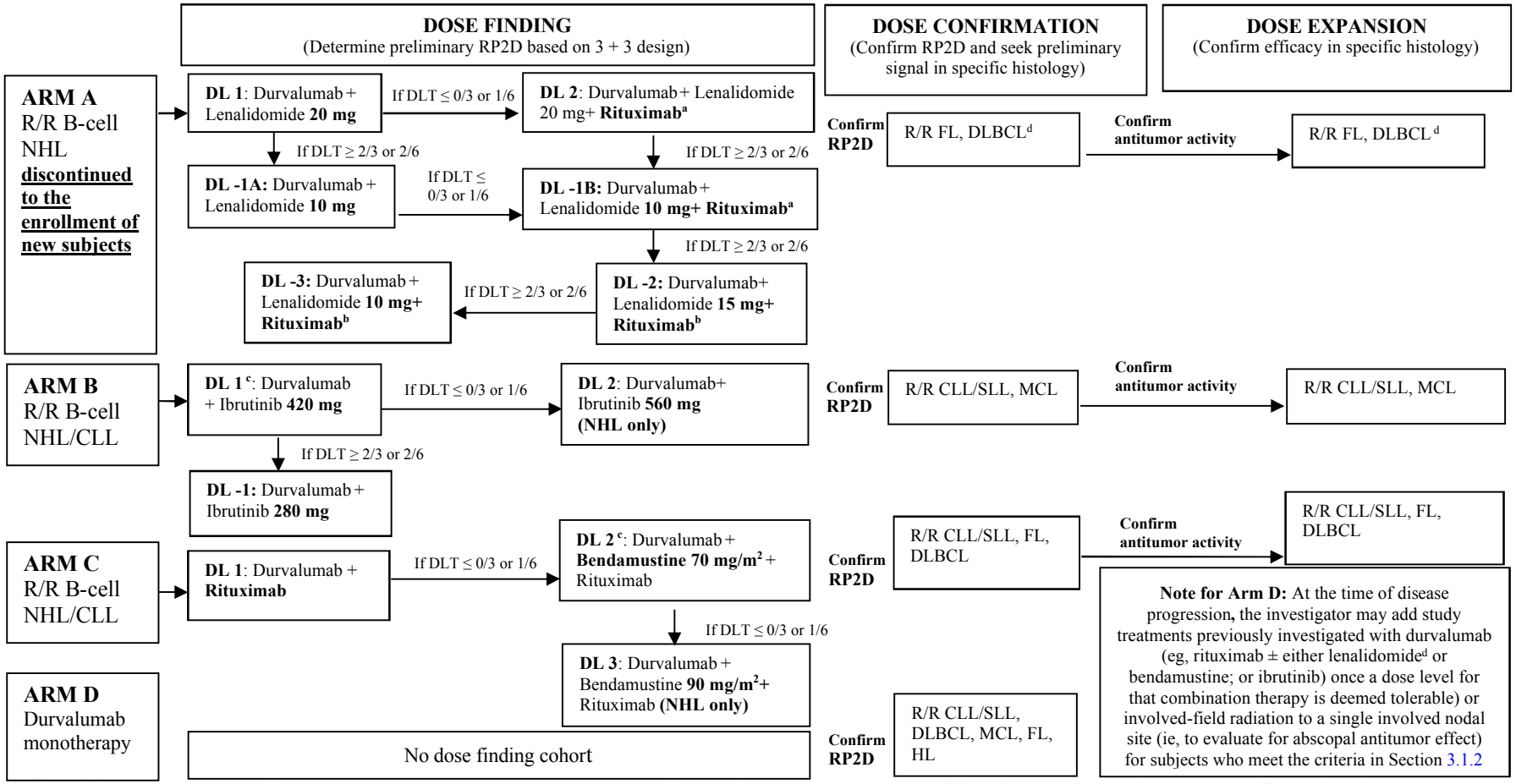
- Arm A (durvalumab and lenalidomide ± rituximab): **discontinued to the enrollment of new subjects. Only those subjects already enrolled and treated who are receiving clinical benefit, based on the discretion of the investigator, may continue study treatment after being reconsented.**
- Arm B (durvalumab 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) in parallel.

All treatment arms will open for enrollment at study start except in the US, where Arm D will enroll depending on the availability of treatment slots and following the completion of assessment of responses from the combination therapy arms (ie, Arms A, B, and C).

Please see the following figure for the overall study design and table for the eligible histologies.

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 DL -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). **Arm A is discontinued to the enrollment of new subjects**. **Only those 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.**

Eligible Histologies per Treatment Arm and Part of the Study

Treatment Arm	Dose Finding (RP2D)	Dose Finding	Evaluation of the Safety of RP2D in Specific Histology and Preliminary Signal Seeking	Dose Confirmation[ab]	Preliminary Efficacy	Dose Expansion[abe]
Arm A[c] (Durvalumab + Lenalidomide ± Rituximab) **Discontinued to the enrollment of new subjects**		R/R B-cell NHL N = 6-30		R/R FL N = 10[d] R/R DLBCL N = 10[d]		R/R FL N = 15[d] R/R DLBCL N = 15[d]
Arm B (Durvalumab + Ibrutinib)		R/R B-cell NHL/ CLL N = 6-12		R/R CLL/SLL N = 10 R/R MCL N = 10		R/R CLL/SLL N = 15 R/R MCL N = 15
Arm C (Durvalumab + Rituximab ± Bendamustine)		R/R B-cell NHL/ CLL N = 3-18		R/R CLL/SLL N = 10 R/R FL N = 10 R/R DLBCL N = 10		R/R CLL/SLL N =15 R/R FL N = 15 R/R DLBCL N = 15
Arm D (Durvalumab)		No dose finding		R/R CLL/SLL R/R DLBCL R/R FL R/R MCL R/R HL N = 30 (5-10 subjects in each histology)		Not planned

Abbreviations: CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin lymphoma; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; N = number of subjects; RP2D = recommended Phase 2 dose; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma.

[a] Subjects with FL Grade 3b may be enrolled into DLBCL cohorts but are excluded from FL cohorts.

[b] Subjects with DLBCL not otherwise specified or T-cell/histiocyte rich large B-cell lymphoma will be eligible for the dose confirmation and expansion DLBCL cohorts.

[c] Arm A will exclude subjects with CLL/SLL.

[d] Arm A dose confirmation and dose expansion cohorts are discontinued and will not enroll new subjects.

[e] Celgene decided to not continue with the dose expansion part of the study.

In the dose finding part (Phase 1), a preliminary RP2D will be established for each durvalumab combination treatment using a 3 + 3 design (Storer, 1989). 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. Three to 6 subjects will be evaluated in each dose finding cohort; therefore, approximately 15 to 60 (DLT evaluable) subjects with B-cell non-Hodgkin lymphoma (NHL) or CLL are anticipated to be enrolled in the dose finding part (6 to 30 subjects in Arm A; 6 to 12 subjects in Arm B; and 3 to 18 subjects in Arm C). 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 dose limiting toxicities (DLTs) observed within each cohort.

A safety review committee (SRC) whose members include the sponsor's medical monitor, drug safety physician, and a subset of investigators will determine a preliminary RP2D for each combination treatment arm (except Arm D) based on the assessment of the safety, available PK and Pd data, and preliminary efficacy information as needed.

In the dose confirmation part (Phase 1), once the preliminary RP2D is established, each combination treatment arm will enroll approximately 10 subjects with each prespecified disease histology (7 cohorts of 10 subjects) into Arms A, B, and C to confirm the tolerability and safety of the RP2D and 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. In total, approximately 100 subjects are anticipated to enroll in the dose confirmation part.

If a promising antitumor signal is detected in any dose confirmation cohort, that cohort will expand and enroll approximately 15 additional subjects to further assess the efficacy in the dose expansion part (Phase 2). In total, approximately 105 subjects are anticipated to enroll in the dose expansion part.

Study Population

Eligible subjects must have previously received treatment with at least one systemic therapy and currently have relapsed or refractory lymphoma or CLL (high risk) 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 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Guidelines for the Diagnosis and Treatment of CLL (Hallek, 2008); (Appendix H). All subjects must have adequate liver, renal, and bone marrow function as defined in Section 4.

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 first dose administered, 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 treatment due to unacceptable toxicity or other reasons.

Once subjects complete the Treatment Period, they will enter into 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. 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 and/or exploratory 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, prior antilymphoma/CLL therapy, and treatment arm/slot availability.

Arm A is discontinued to the enrollment of new subjects, and 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.*

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:

- **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, follicular lymphoma [FL] or marginal zone lymphoma [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 and -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.
- **Arm B:** Ibrutinib (PO) continuous, once daily until disease progression, unacceptable toxicity, starts new therapy, or discontinuation for any other reason, ie, subject withdraws consent or discontinues per investigator's discretion.
- **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.
- **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, or subjects can

receive involved-field radiation to a single involved nodal site (ie, to evaluate for a systemic abscopal antitumor effect) if they meet the criteria defined in Section 3.1.2. Prior to addition of another therapy to durvalumab, the investigator must consult with the sponsor's medical monitor.

Treatment arms and dose levels for each arm are described and tabulated in Section 7 and 9.3.

Overview of Key Efficacy Assessments

Disease response to treatment in lymphoma is determined by the Lugano Classification (Cheson 2014) and in CLL by the modified IWCLL Response Criteria (Hallek, 2008; Hallek, 2012; Hallek, 2013) including a careful review of laboratory assessments (eg, complete blood counts with differential, bone marrow/tumor biopsy assessments, immunophenotyping of blood for circulating CLL cells) and imaging studies (eg, CT or fluorodeoxyglucose-positron emission tomography [FDG-PET] scan) as well as clinical findings (eg, physical examination, constitutional symptoms).

Integrated FDG-PET with CT (FDG-PET-CT) is preferred for response assessment of FDG-avid lymphomas (eg, DLBCL, Hodgkin lymphoma [HL], or FL), while dedicated CT scan alone is preferred for FDG-non-avid and variably FDG-avid histologies (eg, CLL/SLL, or MZL).

Overview of Key Safety Assessments

Safety assessments include monitoring for AEs; physical examination; vital signs and body weight measurement; Eastern Cooperative Oncology Group (ECOG) performance status; hepatitis B virus (HBV) screening; hematology (complete blood count [CBC] with differential and platelets); serum chemistry; urinalysis; serum immunoglobulins; concomitant medications, therapies, and procedures; pregnancy testing (for female subjects of childbearing potential [FCBP] only); and electrocardiogram.

Safety assessments will be performed during screening and will be repeated weekly in Cycle 1, bi-weekly in Cycles 2 through 4 in Arms A, B, D or Cycles 2 through 6 in Arm C, and once every 4 weeks thereafter for all arms. For subjects continuing on ibrutinib, assessments will be performed per the investigator's discretion following standard of care.

The investigator remains responsible to monitor safety, record adverse events (AEs)/serious adverse events (SAEs)/second primary malignancies(SPMs) in source documents, and report SAEs and SPMs to Celgene Drug Safety.

Overview of Pharmacokinetic Assessments

Serum or plasma samples will be collected to assay concentrations of durvalumab and other combination agents (ie, lenalidomide or ibrutinib).

Overview of Biomarker Assessments

Pharmacodynamic markers for durvalumab and other combination agents will be measured, such as soluble programmed cell death ligand 1 (sPD-L1) levels for durvalumab and proliferation of immune cell subsets, and soluble cytokines and chemokines.

Exploratory biomarkers predictive of response or disease/mechanistic related will be measured including, but not limited to PD-L1 protein levels, immune cell subsets, and other markers that

may be associated with immune status, gene signature related to immune-related pathways or cell of origins, T-cell receptor clonality, neoantigen assessments, or genetic alterations.

Overview of Immunogenicity Assessments

Blood samples for immunogenicity will be collected from all subjects. Antidrug antibody (ADA) for durvalumab will be explored using these samples.

Statistical Methods

There are 3 treatment arms in the dose finding part, ie, Arm A (discontinued to the enrollment of new subjects), Arm B, and Arm C. The standard 3 + 3 design will be used to identify the maximum tolerated dose (MTD) and preliminary RP2D in each treatment arm. The sample size for the dose finding part (Phase 1) is expected to range from approximately 15 to 60 (DLT evaluable) subjects. The final number of subjects will depend on the number of dose levels studied and number of DLTs observed within each cohort.

The planned sample size for the dose confirmation (Phase 1) and dose expansion (Phase 2) parts is based on clinical, empirical, and practical considerations traditionally used for Phase 1/2 studies. Please see Section 9.3 for further details.

Should the stopping rules described in Table 34 for the dose confirmation part be fulfilled, the SRC for that cohort and global scientific steering committee (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.

For the efficacy analysis, in order to make use of all available data, the data from the dose expansion and dose confirmation parts will be pooled together for a particular histology for the evaluation of treatment efficacy. A total of approximately 25 subjects in a particular treatment arm and subject histology cohort will provide a moderate estimate of the response rate with 95% confidence interval (CI) no wider than ± 20%. Efficacy analyses will also be performed separately for the dose confirmation part and the dose expansion part as well.

The safety analysis will include all subjects in the safety population.

All analyses will use descriptive statistics.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1. Disease Background

Lymphoid neoplasms originate from cells that normally develop into B lymphocytes (lymphocytes or plasma cells) or T lymphocytes (cytotoxic T lymphocytes, helper T lymphocytes, or regulatory T lymphocytes).

In the 2008 World Health Organization (WHO) classification of lymphoid neoplasms (Swerdlow, 2008), the diagnosis of the various lymphoid neoplasms depends not on the anatomic location of tumor cells, but rather on the cell of origin of the tumor, as judged by morphology, immunophenotype, and genetic findings. As a result, several entities previously considered distinct are now grouped together under single diagnostic categories (eg, chronic lymphocytic leukemia [CLL] and small lymphocytic lymphoma [SLL]).

1.1.1. Non-Hodgkin Lymphoma and CLL

Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of lymphoproliferative neoplasm with differing patterns of behavior and responses to treatment (Armitage, 1993). Currently, the WHO Lymphoma Classification scheme is utilized to define specific subtypes of lymphoma and subdivides them based on cell of origin (B, T or natural killer [NK]) and whether they are derived from precursor lymphocytes versus mature lymphocytes (Swerdlow, 2008). Most (ie, 80% to 90%) NHLs are of B-cell origin. In the United States (US), 80-85% of lymphomas are diagnosed as B-cell lymphomas and 15% to 20% as T-cell lymphomas. Natural killer-cell lymphomas are very rare.

The pathogenesis of lymphomas represents a complex process involving the accumulation of multiple genetic lesions affecting proto-oncogenes and tumor suppressor genes. The lymph node microenvironment, which includes stromal cells, macrophages, regulatory T-cells, and the lymph node vasculature, has been implicated in the promotion of lymphomagenesis (Coupland, 2011).

In 2015, it is estimated that there will be 71,850 new cases of NHL and an estimated 19,790 people will die from this disease annually in the US (Siegel, 2015).

Chronic lymphocytic leukemia is the most common leukemia in North America and Europe with an incidence of 4.0 cases per 100,000 persons per year and has a median age of diagnosis of 72 years. It consists of an accumulation of mature B-cells typically cluttering in marrow, blood and lymphoid organs with a unique cluster of differentiation (CD) 19+, CD5+, and CD23+ phenotype. The etiology of CLL is unknown and its pathogenesis is not clearly understood, however it is likely that the following factors play a significant role: accumulation of genomic events over time, chronic antigen stimulation, and age-related changes in immunosurveillance and in the tumor microenvironment.

Chronic lymphocytic leukemia is a heterogeneous disease with a variable disease course from indolent disease (at times requiring little to no therapy) to aggressive disease (fatal disease poorly responsive to aggressive therapeutic intervention). Prognostic factors in CLL include clinical, serum, genetic, as well as cytogenetic markers.

1.1.2. Hodgkin Lymphoma

Hodgkin lymphoma (HL), formerly called Hodgkin's disease, arises from germinal center or post-germinal center B-cells. Hodgkin lymphoma has a unique cellular composition, containing a minority of neoplastic cells (Reed-Sternberg cells and their variants) in an inflammatory background. It is separated from the other B-cell lymphomas based on its unique clinicopathologic features.

Hodgkin lymphoma is a B-cell lymphoma that accounts for approximately 10% of all lymphomas in economically advanced countries. This amounts to approximately 9,050 new cases and about 1,150 deaths due to HL in the US annually (Siegel, 2015). The incidence in Europe is approximately 2.4 cases per 100,000 persons (Sant, 2010; Smith, 2011).

The treatment of patients with HL is primarily guided by the clinical stage of disease as determined by the Cotswolds classification (Lister, 1989). While the majority of treated patients will be cured of their lymphoma, treatment-related toxicities have become a contributing cause of mortality later in life. As such, the selection of therapy must balance the desire to maintain a high rate of cure and the need to minimize long-term complications.

Recent major advances in the therapeutic field have been the results of treatment strategies utilizing agents that target unique antigens (eg, anti-CD30-drug immunoconjugate [brentuximab vedotin], check-point inhibition via anti-programmed cell death-1 (anti-PD-1) monoclonal antibodies [nivolumab, pembrolizumab, and pidilizumab]) which have antitumor activity in patients with R/R HL. Although these novel agents appear to prolong patient survival, they are not curative.

Despite the progress in treatment outcomes for lymphoma or CLL, largely secondary to the addition of novel targeted or biologic-based therapies in recent years, a high percentage of patients experience R/R disease. Overall, lymphoma or CLL remains mostly incurable in the majority of patients treated with conventional therapies. New therapies are urgently needed to treat R/R lymphoma or CLL patients.

1.2. Compound Background

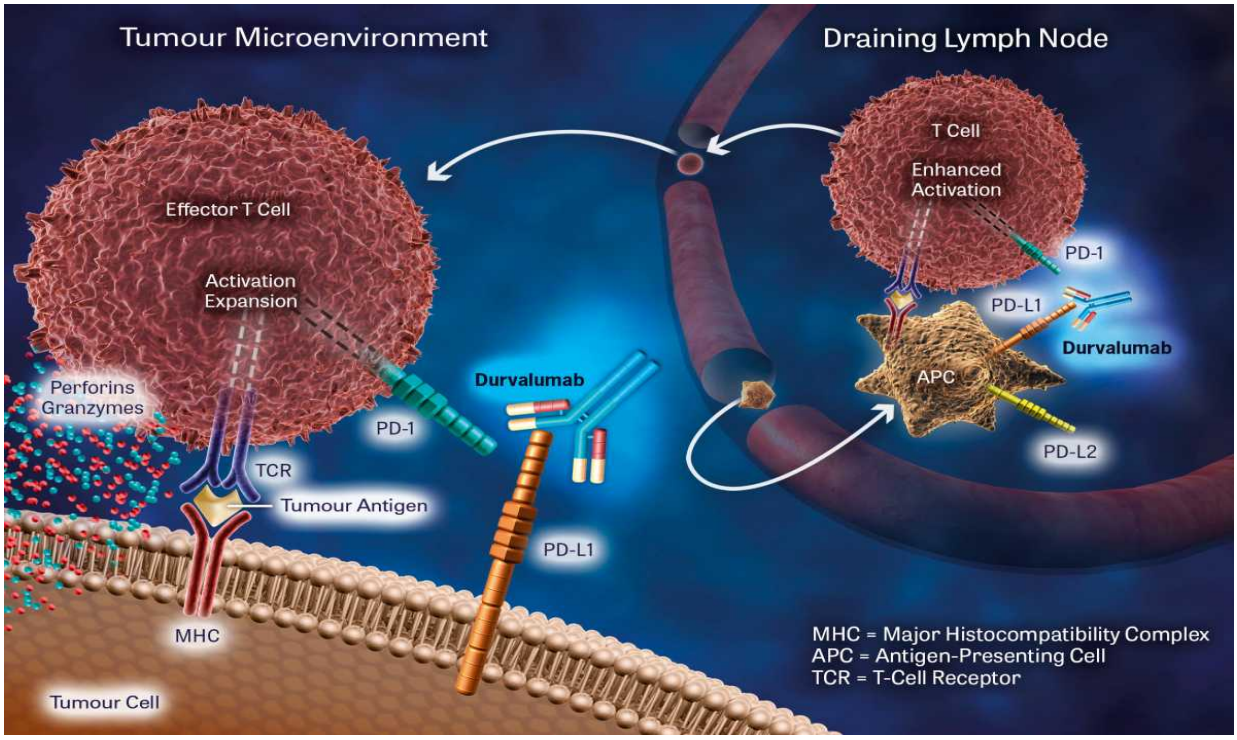
1.2.1. Durvalumab (MEDI4736)

Durvalumab (MEDI4736) is a human immunoglobulin (Ig) G1κ monoclonal antibody (mAb) that blocks programmed cell death ligand-1 (PD-L1) by binding to its receptors, allowing T-cells to recognize and kill tumor cells as illustrated in Figure 1. Durvalumab selectively binds to human PD-L1 with high affinity and blocks its ability to bind to programmed cell death-1 (PD-1) and cluster of differentiation (CD80). The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fcγ receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC) (Oganesyan, 2008; Ibrahim, 2015).

On 01 May 2017, the US FDA granted accelerated approval to durvalumab (IMFINZI™) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Please refer to the Durvalumab Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of investigational product (IP).

Figure 1: Mechanism of Action of Durvalumab (MEDI4736; an Anti-PD-L1 Antibody)



PD-L1 inhibits cancer immunity (Zou, 2008)
Durvalumab binds to PD-L1 and allows T-cells to recognize and kill tumor cells (Segal, 2014)
Durvalumab is a selective, high affinity human IgG mAb that blocks PD-L1 binding to PD-1 (IC_{50} 0.1 nM) and CD80 (IC_{50} 0.04 nM) (Segal, 2015)

1.2.2. Lenalidomide

Lenalidomide (Revlimid®) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiD®) and has potent immuno-stimulatory, antiangiogenic, and pro-apoptotic activities in vitro.

In the US, lenalidomide has been approved for the treatment of patients with MM in combination with dexamethasone and in monotherapy as maintenance following autologous stem cell transplantation; transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities; and mantle cell lymphoma (MCL) whose disease has relapsed or progressed after 2 prior therapies, one of which included bortezomib.

In Europe, lenalidomide has been approved as monotherapy for maintenance treatment of patients with newly diagnosed MM who have undergone autologous stem cell transplantation; as combination treatment of patients with previously untreated MM who are not eligible for transplant; in combination with dexamethasone for the treatment of patients with MM who have received at least one prior therapy; transfusion-dependent anemia due to low- or intermediate-1-

risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate; and relapsed or refractory (R/R) MCL.

Please refer to the Lenalidomide Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the IP.

1.2.3. Ibrutinib

Ibrutinib (Imbruvica®) is an inhibitor of Bruton's tyrosine kinase (BTK). Bruton's tyrosine kinase is a non-receptor tyrosine kinase with restricted cellular expression largely limited to B-lymphocytes, monocytes and mast cells or basophils. Bruton's tyrosine kinase is a critical component of the B-cell receptor signaling network and is crucial for B-cell development.

In the US, ibrutinib has been approved for the treatment of patients with MCL who have received at least one prior therapy; CLL/SLL; CLL/SLL with 17p deletion; Waldenstrom's macroglobulinemia; and marginal zone lymphoma who require systemic therapy and have received at least one prior anti-CD20 based therapy.

In Europe, ibrutinib has been approved for the treatment of patients with R/R MCL; previously untreated CLL; CLL who have received at least one prior therapy as a single agent or in combination with bendamustine and rituximab; and Waldenstrom's macroglobulinemia who have received at least one prior therapy, or in first line for patients unsuitable for chemoimmunotherapy.

Ibrutinib is currently being studied in multiple histologies as monotherapy or in combination therapy.

1.2.4. Bendamustine

Bendamustine (Treanda®, Bendeka®, Levact®) is an alkylating drug whose mechanisms of action involve induction of apoptosis through activation of DNA-damage stress responses, inhibition of mitotic checkpoints, and induction of mitotic catastrophe (Leoni, 2008).

In the US, bendamustine has been approved for the treatment of patients with CLL (efficacy relative to first line therapies other than chlorambucil has not been established) and indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.

In Europe, bendamustine has been approved for the treatment of patients with CLL for whom fludarabine combination chemotherapy is not appropriate and indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen as well as front-line treatment of MM in combination with prednisone for patients older than 65 years of age.

1.2.5. Rituximab

Rituximab (Rituxan®, MabThera®) is a cytolytic, chimeric murine/human monoclonal antibody directed against the CD20 cell-surface molecule present (CD20+) in normal B lymphocytes and B-cell CLL and in most forms of non-Hodgkin B-cell lymphomas.

In the US, rituximab has been approved for the treatment of patients with R/R low grade or follicular lymphoma (FL), CD20+, B-cell NHL as single agent; for the treatment of patients with previously untreated FL, CD20+, B-cell NHL in combination with first line chemotherapy; for the treatment of patients who have achieved a complete or partial response to rituximab in combination with chemotherapy, as single agent maintenance therapy; for the treatment of patients non progressing (including stable disease), low grade, CD20+, B-cell NHL as a single agent after first line cyclophosphamide, vincristine, and prednisone chemotherapy; for the treatment of patients with previously untreated diffuse large B-cell lymphoma (DLBCL), CD20+ NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy or other anthracycline-based chemotherapy regimens; and for the treatment of patient with previously untreated and previously treated CD20+ CLL.

In Europe, rituximab has been approved for the treatment of patients with previously untreated stage 3 and 4 FL in combination chemotherapy; for the treatment of patients with FL patients responding to induction therapy; for the treatment of patients with stage 3 and 4 FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy; for the treatment of patients with CD20+ DLBCL NHL in combination with CHOP chemotherapy; and for the treatment of patients with previously untreated and R/R CLL.

Rituximab has been also approved for non oncology indications (ie, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis) in the US and Europe.

1.3. Rationale

1.3.1. Immune-checkpoint Inhibition

Tumor-infiltrating lymphocytes (TILs) have the capacity to control the growth of many types of cancers (Gooden, 2011). Most tumors show infiltration by TILs, but tumors modulate the local microenvironment through expression of inhibitory molecules. Engagement of TIL cell-surface receptors with these inhibitory ligands leads to a dysfunctional immune response, causes T-cell exhaustion, and facilitates tumor progression (Baitsch, 2012; Crespo, 2013). It is increasingly appreciated that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors (Dunn, 2004). Novel monoclonal antibodies (mAbs) that block these inhibitory receptors have shown significant clinical activity across a number of tumor types (Wolchok, 2009; Hodi, 2010; Robert, 2011; Brahmer, 2010; Topalian, 2012). Specifically, blockade of immune-checkpoint inhibitors such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), PD-1, and PD-L1 have shown clinical activity not only in conventionally immune-responsive tumors such as melanoma and renal cell carcinoma but also in non-small cell lung cancer (Brahmer, 2010; Brahmer, 2012; Topalian, 2012; Gordon, 2013) and prostate cancer (Harzstark, 2010).

Pembrolizumab and nivolumab are both PD-1 blocking antibodies and the first in the anti-PD-1 pathway family of checkpoint inhibitors to gain regulatory approval from the US FDA and European Commission for melanoma and non-small cell lung cancer (NSCLC). Nivolumab has also been approved for melanoma in combination therapy with ipilimumab, another checkpoint inhibitor (anti-CTLA-4 antibody). Both anti-PD-1 antibodies (nivolumab and pembrolizumab) have gained approvals for additional indications from the US FDA and/or the European Commission (ie, nivolumab for renal cell carcinoma from the FDA and European Commission;

pembrolizumab for head and neck squamous cell carcinoma from the FDA; nivolumab and pembrolizumab for classical HL from the FDA and European Commission).

In Japan, both pembrolizumab and nivolumab have been approved for melanoma and non-small cell lung cancer. Nivolumab has also been approved for renal cell carcinoma and classical HL in Japan.

Atezolizumab, an anti-PD-L1 antibody, has been approved by the US FDA for the treatment of patients with locally advanced, or metastatic urothelial carcinoma whose disease has worsened during, or following platinum-containing chemotherapy, or within 12 months of receiving platinum-containing chemotherapy, either neoadjuvant or adjuvant surgical treatment as well as for the treatment of patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy, and have progressed on an appropriate FDA approved targeted therapy if their tumor has epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) gene abnormalities.

Several anti-PD-1 and anti-PD-L1 antibodies are currently being studied in multiple other oncologic and hematologic indications either as monotherapy or in combination therapy.

1.3.2. Study Rationale and Purpose

Lymphoma/CLL is comprised of multiple histologies. It is hypothesized that durvalumab will have activity in multiple indications based on known expression pattern of PD-L1/PD-1, available preclinical data, and recent clinical data utilizing nivolumab (Ansell, 2015) or pembrolizumab (Moskowitz, 2014) in R/R classical HL and promising early data of pidilizumab alone or in combination with rituximab (Westin, 2014) in DLBCL or FL, respectively; also nivolumab monotherapy (Lesokhin, 2014) has shown antitumor activity in DLBCL, FL, and T-cell lymphomas.

The programmed cell death-1 (PD-1) plays an important role in the regulation of the immune response. The PD-1 receptor, in conjunction with receptor ligands PD-L1 and PD-L2, functions to regulate the immune system primarily by down regulating signals of the T-cell receptor. PD-L1 expressed on tumor cells binds to PD-1 on T-cells which leads to down-regulation of T-cell activity and allows tumor cells to evade the immune response.

Based on in vitro studies, an antibody that blocks the interaction between PD-L1 and its receptors can relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of antitumor T-cells (Blank, 2007). The levels of tumor-infiltrating lymphocytes, and more specifically cytotoxic T-cells, have been correlated with improved prognosis in a number of cancers including colorectal, melanoma, and lung (Galon, 2006; Clemente, 1996; Dieu-Nosjean, 2008, Hodi 2010). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in multiple forms of cancer. Results of several preclinical studies using mouse myeloma models support this hypothesis (Gorgun, 2015; Hirano, 2005; Iwai, 2002; Kearl, 2013; Okudaira, 2009; Zhang, 2008). In these studies, antibodies directed against PD-L1 or its receptor, PD-1, demonstrated antitumor activity by inducing anti-MM immune responses. In addition to the limited aforementioned clinical data in NHL with agents that inhibit PD-1, there are several other preclinical and prognostic observations in various lymphoma subtypes that lead us to believe that PD-1/PD-L1 inhibition may prove to be efficacious:

- Two recently published Blood journal articles describing PD-L1/PD-1-mediated CD8 T-cell dysfunction in the context of aging-related immune defects in a CLL mouse model which replicates human T-cell defects (McClanahan, 2015; McClanahan, 2015a) and that utilizing the same murine CLL mouse model that in vivo PD-L1 blockade normalizes T-cell and myeloid cell populations and immune effector functions and prevents CLL development following adoptive transfer.
- A large French multicenter clinical trial demonstrated that high levels of plasma soluble PD-L1 are associated with a poorer prognosis (ie, overall survival [OS]) in DLBCL patients treated with R-CHOP and are a patient predictive biomarker; use of PD-1 axis inhibitors may prove to be effective in this subgroup of DLBCL patients (Rossille, 2014).
- PD-1 expression in peripheral blood CD4+ and CD8+ T-cells were found to be markedly different between CLL disease stages when compared with healthy subjects; highest numbers of both CD8+ PD-1+ and CD4+PD-1+ cells were present in R/R CLL patients (Novak, 2015).
- A preclinical model demonstrated that PD-L1 expressed on MCL cells inhibited T-cell proliferation, impaired antigen-specific T-cell responses, and rendered MCL cells resistant to T-cell mediated cytolysis which could be reversed by blocking or knocking down tumor cell-associated PD-L1 (Wang, 2013).

In this current trial a diverse group of lymphoma histologies (eg, R/R CLL and B-NHL) will be evaluated in both durvalumab monotherapy and durvalumab combination therapy arms in an attempt to determine dose finding/ safety, but also which lymphoma histology and treatment arms show the strongest antitumor signals which will lead to additional clinical trials.

1.3.3. Rationale for the Study Design

The safety of durvalumab has already been explored and assessed in other hematology and oncology patient populations. No dose limiting toxicity has been defined to date. Dosing was originally based on weight and ranged up to 10 mg/kg once every 2 weeks (Q2W) and 20 mg/kg once every 4 weeks (Q4W). Pharmacokinetic analysis demonstrated that fixed dosing had equivalent variability to weight based dosing. Based on an average weight of 75 kg, a fixed dose of 1500 mg Q4W is now being explored as a dose that provides continuous plasma concentration of antibody above the threshold needed for in vitro activity. The dose of 1500 mg Q4W is the recommended Phase 2 dose (RP2D) across the durvalumab clinical program (for ongoing or planned studies in both solid tumors and hematologic malignancies). Over 1000 patients with solid tumors and myelodysplastic syndrome were treated at a dose schedule equivalent to 1500 mg Q4W (ie, 10 mg/kg Q2W or 20 mg/kg Q4W which show similar exposure levels based on the area under the curves steady state), and available safety data support this as an appropriate dose for durvalumab in this study. Please refer to the Durvalumab IB for further information and Section 1.3.4.

There is no prior clinical experience with durvalumab monotherapy in lymphoma/CLL or in combination with lenalidomide, bendamustine, ibrutinib, or rituximab. A parallel dose-finding/confirmation or expansion design was selected to confirm the safety of the 1500 mg Q4W durvalumab dose as monotherapy and for selected durvalumab combination regimens in

R/R population of lymphoma and CLL patients. A standard 3 + 3 dose finding trial design will be used to evaluate the safety and establish the RP2D of each combination.

Once the RP2D for each combination is established, treatment arms of interest may be expanded to obtain additional safety, pharmacokinetics (PK), pharmacodynamics (Pd) and efficacy data in specific lymphoma histologies and CLL, and thereby to guide future development.

1.3.4. Rationale for Dose, Schedule, and Regimen Selection

The dose and schedule for durvalumab monotherapy (20 mg/kg Q4W) were selected based on 2 sets of data: (i) the safety analysis of doses (0.1, 0.3, 1, 3, and 10 mg/kg Q2W) administered in Study CD-ON-MEDI4736-1108 (a Phase 1/2 study to evaluate the safety, tolerability, and PK of durvalumab IV given as monotherapy in subjects with advanced solid tumors); and (ii) PK profile simulations for durvalumab administered using 10 mg/kg Q2W and 20 mg/kg Q4W schedules.

Safety and PK characteristics of the studied dose and schedule 10 mg/kg Q2W:

After evaluation of the PK data from subjects enrolled in Study CD-ON-MEDI4736-1108, durvalumab exhibited nonlinear (dose dependent) PK consistent with target-mediated drug disposition. Linear PK was observed at doses of 3 mg/kg and higher and is consistent with near complete target suppression, as reflected in target trough plasma concentrations of drug > 100 ug/mL. This trough concentration is supported by soluble PD-L1 (sPD-L1) suppression data. Furthermore, the 10 mg/kg Q2W dose was not associated with any dose limiting toxicities (DLTs) in the dose escalation portion and was, therefore, selected for further evaluation in the dose expansion portion of Study CD-ON-MEDI4736-1108.

Extrapolation of dose and schedule of 10 mg/kg Q2W to 20 mg/kg Q4W through population PK modeling:

A population PK model was developed using durvalumab monotherapy data from Phase 1 of Study CD-ON-MEDI4736-1108 (N = 292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg once every 3 weeks; solid tumors) (Fairman, 2014). This population PK model adequately described monotherapy PK data and was utilized to predict expected PK exposures following 20 mg/kg Q4W dosing regimens (since none of the monotherapy studies explored Q4W regimens). Pharmacokinetic simulations indicate that a similar overall exposure as represented by area under the curves steady state (AUC_{ss}) (4 weeks) is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens. However, median maximum plasma concentration (C_{max}) at steady state is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median trough concentration at steady state is expected to be higher with 10 mg/kg Q2W (~1.25 fold).

Justification for fixed dosing over weight-based dosing:

Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed-dosing regimens yield similar median

steady state PK concentrations with slightly less overall between-subject variability with the fixed- dosing regimen.

Similar findings have been reported by others (Ng, 2006; Wang, 2009; Zhang, 2012; Narwal, 2013). Wang and colleagues (Wang, 2009) investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they (Zhang, 2012) investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 proteins in terms of reducing the between-subject variability in PK/Pd parameters.

A fixed-dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed-dosing regimens. Based on average body weight of 75 kg, a fixed dose 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is the RP2D for this study.

Please refer to the Durvalumab IB for further information.

1.3.5. Rationale for Choice of Combination Compounds

1.3.5.1. Rituximab and Lenalidomide

Lenalidomide has pleiotropic activities including a capacity to activate NK cells, to increase T-cell proliferation and function, and to enhance macrophage-mediated ADCC of rituximab-coated tumor cells. The main molecular target of lenalidomide is the E3 ubiquitin ligase cereblon that was recently shown to trigger induction of cytokine production by T-cells. Follicular lymphoma infiltrating CD4+ and CD8+ tumor induced immunosuppression in the context of increased expression of B7- related inhibitory ligands (including PD-L1) down-regulates activated Rho-GTPases RhoA, Rac1, and Cdc42, key regulators of T-cell synapse actin dynamics. T-cells display immunological synapse dysfunction with impaired F-actin polymerization and reduced effector function. Lenalidomide can repair the Rho A mediated T-cell synapse defect present in cancer patients thereby restoring T-cell functions and potentially enabling the effect of immunotherapies (Greaves, 2013; Ramsay, 2013; Gribben, 2015).

Lenalidomide clinical trials with registration intent are ongoing with the combination of lenalidomide and rituximab in relapsed, refractory and first line FL, based on Phase 2 results suggesting that this combination may be a reasonable alternative to traditional chemo-immunotherapy (Fowler, 2014; Leonard, 2015)

Preclinical studies with respect to MM have demonstrated that lenalidomide enhances immune checkpoint blockade (ie, anti- PD-1/PD-L1) induced immune response in patient-derived primary myeloma cells; this may represent a novel immune-based therapeutic strategy to treat MM and other B-cell neoplasms (Gorgun, 2015). Other studies demonstrate that lenalidomide reduced PD-L1 expression on myeloma cells (Benson, 2010), and that lenalidomide exposure resulted in a decrease in the expression of PD-1 on T-cells and induced amplified responses to myeloma vaccine (Luptakova, 2013).

1.3.5.2. Ibrutinib

Ibrutinib is a covalent BTK inhibitor which affects 3 key neoplastic B-cell processes: a) inhibits proliferation/survival; b) inhibits adhesion; and c) modulates chemotaxis. It is US FDA approved for patients with 17p-deletion CLL and for CLL or MCL patients who have received at least one prior therapy. Ibrutinib has also demonstrated preferential clinical response activity in activated B-cell-like versus germinal center B-cell like DLBCL in a monotherapy clinical trial of relapsed DLBCL (Wilson, 2015) as well as moderate single-agent activity in R/R FL (Fowler, 2012). Recently, Stanford University investigators demonstrated that the combination of anti-PD-L1 antibodies and ibrutinib suppressed tumor growth in mouse models of lymphoma insensitive to ibrutinib and enhanced antitumor T-cell immune responses, based in part on the ability of ibrutinib to inhibit interleukin-2-inducible T-cell kinase and thus potentially enhance T helper 1 based immune responses (Sagiv-Barfi, 2015). These findings, along with ibrutinib's favorable toxicity profile, make it a good choice to study in combination with durvalumab in a variety of lymphoma histologies.

1.3.5.3. Bendamustine and Rituximab

Bendamustine is an alkylating agent which structure also shows similarities to purine analogues. It has antitumor activity in both hematologic and solid tumors. The combination of bendamustine and rituximab is highly utilized clinically to treat FL, CLL/SLL, and MCL around the world.

Of interest, a Phase 2 multicenter study of bendamustine and rituximab in older patients with previously untreated DLBCL (N = 23) demonstrated an overall response rate of 93% (complete response [CR] rate of 60%) in 15 evaluable patients with a time to progression of 7.4 months (Spina, 2014); in addition, 2 small clinical trials of bendamustine and rituximab in R/R DLBCL demonstrated an overall response rate (ORR) of 50 to 60% and a median progression-free survival (PFS) of approximately 7 months (Arcari, 2014; Ohmachi, 2013). Bendamustine has also been used in R/R FL, MCL, and other indolent lymphomas (Rummel, 2005) as well as CLL (Fischer, 2011).

It may seem counterintuitive to use bendamustine in a trial initializing an anti PD-L1 monoclonal antibody. The use of rituximab maintenance therapy following bendamustine plus rituximab induction in lymphoma has been shown to be associated with sustained CD4 lymphopenia (Yutaka, 2015); however, it appears that fludarabine and rituximab based therapy (without rituximab maintenance) in low grade lymphoma appears to result in an even longer recovery time for circulating T-cells in peripheral blood (Czuczman, 2005). The correlation of T-cell subsets between blood versus marrow/nodal compartments and their changes following exposure to durvalumab is unknown and is part of the correlative studies on this trial. It may be hypothesized that T-cells within the tumor/marrow microenvironment may still be present and responsive to agents targeting the PD-1/PD-L1 axis (even if they are significantly decreased or even absent in peripheral blood).

1.3.5.4. Local Involved Field Radiation Therapy

The addition of other antilymphoma/CLL agents (ie, those shown to be safe in combination with durvalumab [Arms A, B, or C]) or "involved-field" radiation therapy (IFRT) (to evaluate for possible abscopal effect) at the time of progressive lymphoma or CLL is allowed as an option in

this study. B-cell lymphoma is a highly radiosensitive disease. The potential value of combining durvalumab with other agents used in the treatment of lymphoma or CLL is discussed in this section and is self-explanatory. However, the potential benefit of the combination of a check-point inhibitor plus IFRT requires further elucidation.

Immunologic responses to localized radiation therapy leading to systemic antitumor effects in non-radiated tumor sites (called the abscopal effect) is very rare event and largely reported as case studies in the past (Reynders, 2015). Theoretically, recent advances in the field of immune-oncology indicates that significant increase in the incidence of "abscopal" effects may become reality when immune checkpoint inhibitors are combined with limited field radiation therapy (Almo, 2014).

A review on this topic describes the critical role of radiation therapy (with appropriate dose and fraction [not known]) causes an "in situ" vaccination by inducing tumor "neoantigen" release for dendtritic cross-presentation; if this occurs in the setting of immune check-point blocked immunotherapy (eg, anti-PD-L1), the tumor-specific immune response is triggered/enhanced and can lead to a systemic antitumor activity in the host. It is unknown which regimen of radiation therapy is optimal in maximizing this abscopal effect, but it is suggested that hypofractionated radiation therapy may be better than conventional or hyper-fractionated techniques (Teng, 2015).

Therefore, for subjects enrolled in all study arms, at time of progressive lymphoma or CLL, IFRT (to evaluate for possible abscopal effect) is allowed.

1.3.6. Rationale for Pharmacodynamics and Potential Predictive Biomarkers

Durvalumab binds human PD-L1 with high affinity and blocks its ability to bind PD-1. This restores immune activation with downstream effects on cytokine production, proliferation, cell survival, and transcription factors associated with effector T-cell function. Measurements of pharmacodynamic biomarkers, such as soluble PD-L1 saturation and immune cell activation status, could help with understanding the pharmacological effect of durvalumab and contribute to the decision of dose and schedule selection.

A key scientific objective of this clinical study is to evaluate the dynamic changes in the microenvironment of the tumor. While understanding the immunologic characteristics at baseline may be both predictive and prognostic, it will be extremely critical to understand the changes in the local immune system following treatment with durvalumab and the combination agents. Biomarker analysis of durvalumab in NSCLC patients demonstrated a statistically significant increase in CD8+ infiltrating lymphocytes from on-treatment tumor samples compared with pretreatment biopsies (Rizvi, 2015). Furthermore, durvalumab treatment induces IFNγ and effector T-cell and type 1 T-helper (Th-1) cell gene expression within the NSCLC biopsies within 4 to 8 weeks of treatment (Higgs, 2016), indicating a more inflamed tumor microenvironment. This data is consistent with the pharmacodynamic effects observed in tumor biopsies from patients treated with atezolizumab (PD-L1 inhibitor) and pembrolizumab (PD-1 inhibitor). For pembrolizumab, increasing of CD8+ density at tumor or invasive margin after treatment is observed in responders while absent in progressors in melanoma, indicating that the CD8+ TILs were activated and targeting the tumor (Tumeh, 2014). Serial biopsy analyses for atezolizumab showed that increases in PD-L1 protein expression and genes indicative of activated T cells (eg, granzyme, IFNγ) were more frequently observed in patients who respond to the therapy compared with the non-responders (Herbst, 2014). Notably, while pharmacodynamic

response to durvalumab and atezolizumab can also be observed in the blood, circulating biomarkers have not been shown to be correlated with response.

Evaluation of on-treatment tumor samples is critical for identifying pharmacodynamics changes that are induced by durvalumab. These biomarker data will facilitate better understanding of the mechanism of action for durvalumab alone or in combination with other agents to facilitate future clinical study designs. The data will also allow new biomarker development to drive clinical decisions early in patient treatment and reveal new targets/additional immune system pathways that may be targeted to improve therapeutic outcomes.

Pretreatment biopsies will be used to assess biomarkers that may be predictive of response to durvalumab combination therapies. Experience of durvalumab in solid tumors showed that greater responses were observed in subjects with PD-L1-positive, and a much lower rate of responses in subjects with PD-L1-negative tumors (Segal, 2014). Thus, continued evaluation of these biomarkers and a broad exploration of additional biomarkers related to immunological and disease factors are needed to help the identification of potential predictive biomarkers for the therapy.

A number of recent studies have reported correlation between several molecular markers, including expression level of PD-L1 in tumor and immune cells, gene expression patterns, neoantigen presentation and T cell clonality, and the clinical activity of immune checkpoint inhibitors (Topalian, 2012; Herbst, 2014). More recent data indicates that a combination of elevated PD-L1 protein expression and elevated IFNγ gene expression in pretreatment tumor biopsies may predict the best response to durvalumab monotherapy (Higgs, 2015; Higgs, 2016).

Non-Hodgkin lymphoma is a heterogeneous patient population with multiple diseases. Genetic/cytogenetic changes have been shown to be associated with disease prognosis. Gene expression signatures related to cell of origin or other disease mechanism may define disease subtypes with differential response. Baseline disease specific biomarkers such as genetics/gene expression signatures will be measured in the study. The samples collected in the study may be utilized for unbiased genetic/genomic analysis to understand disease or mechanism of action for single or combination therapies.

Multi-color flow cytometry techniques will be used to monitor minimal residual disease (MRD) in MCL and CLL as well as polymerase chain reaction techniques in FL. Newer therapies including novel agents, have increased the partial response (PR) and complete response (CR) rates dramatically in various histologies. Consequently, to adapt treatment intensity, extend duration of response, and prolong progression free survival, more sensitive clinical assessment methods are necessary to better define treatment outcomes at the molecular level. The MRD assessments in MCL, CLL, and FL histologies in this study will be an additional tool for assessment of response and outcome.

Overall, these biomarker data will facilitate better understanding of the mechanism of action for durvalumab alone or in combination with other agents to facilitate future clinical trial designs. The data may also reveal new targets/additional immune system pathways to improve therapeutic outcomes.

2. STUDY OBJECTIVES AND ENDPOINTS

Arm A is discontinued to the enrollment of new subjects. 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.

Table 1: Study Objectives

Primary Objectives
The primary objectives of the study are: **Dose finding part (Phase 1):** • 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 (Phase 1):** • 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 **Dose expansion part (Phase 2):** • To evaluate the preliminary efficacy of durvalumab when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab in subjects with lymphoma or CLL
Secondary Objectives
The secondary objectives are: **Dose finding and confirmation parts (Phase 1):** • 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 **Dose expansion part (Phase 2):** • To assess the safety of durvalumab when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab in subjects with lymphoma or CLL **All parts (Phase 1/2):** • 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

Table 1: Study Objectives (Continued)

Exploratory Objectives
The exploratory objectives are: • To explore population PK analyses including the influence of intrinsic and extrinsic factors that may influence durvalumab exposures • To determine the immunogenicity of durvalumab as monotherapy and when given in combination • To explore the PK/Pd relationship, explore Pd mechanistic biomarkers for durvalumab and other combination agents in the study • To explore host immune and tumor molecular markers predictive of response to durvalumab and other agents when given in combination • To explore minimal residual disease (MRD) and its correlation with clinical outcome • To explore the abscopal effect (ie, immune-mediated tumor response outside the radiation field) of local involved field radiation therapy when given in combination with durvalumab Analyses of well characterized biomarkers (eg, soluble PD-L1 [sPD-L1]) in Arm D) will be fully described in the statistical analysis plan and reported in the clinical study report, while analyses of non-characterized biomarkers will be exploratory and will not be reported in the clinical study report.

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary Endpoints:			
Dose finding (Phase 1)	Safety	Non-tolerated 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 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 (Phase 1)	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 expansion (Phase 2)	Preliminary efficacy: IWG Response Criteria for Malignant Lymphoma (the Lugano Classification) (Cheson 2014) and	Overall response rate (ORR) based on the tumor specific response criteria: ORR (lymphoma): Proportion of subjects with best response of partial response (PR) and complete response (CR)	During durvalumab treatment (up to 13 cycles)
	IWCLL Response Criteria for CLL (Hallek, 2008; Hallek, 2012; Hallek, 2013)	ORR (CLL): Proportion of subjects with best response of CR, CR with incomplete marrow recovery (CRi), nodular PR (nPR), PR, PR with lymphocytosis (PRL)	

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Secondary Endpoints:			
Dose finding and confirmation (Phase 1)	Preliminary antitumor activity:	ORR based on the tumor specific response criteria:	During durvalumab treatment (up to 13 cycles)
	IWG Response Criteria for Malignant Lymphoma (the Lugano Classification) (Cheson 2014)	ORR (lymphoma): Proportion of subjects with best response of PR or CR	
	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	
All parts (Phase 1/2)	Other efficacy parameters:	ORR based on the tumor specific response criteria:	During the study
	IWG Response Criteria for Malignant Lymphoma (the Lugano Classification) (Cheson 2014)	ORR (lymphoma): Proportion of subjects with best response of PR or CR	
	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	
	Time to first response (TTR)	TTR (lymphoma): Time from first IP dose to the first documented response (PR or CR) TTR (CLL): Time from first IP dose to the first documented response (CR, CRi, nPR, PR, or PRL)	

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	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	
	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
Dose expansion (Phase 2)	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
All parts (Phase 1/2)	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
	Pd	Individual soluble PD-L1 (sPD-L1) in blood at baseline and at specified time points (monotherapy)	During the study treatment
Exploratory Endpoints:			
All parts (Phase 1/2)	Population PK	Assessed by nonmixed effect modeling (NMEM) compartment analysis	During Cycles 1 & 2
All parts (Phase 1/2)	Immunogenicity	The number of subjects who develop anti-drug antibody (ADA) against durvalumab	During durvalumab treatment

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
All parts (Phase 1/2)	Pd	Pharmacodynamic biomarkers include but are not limited to gene and/or protein expression of analytes, such as individual sPD-L1 levels and immune cell activation in peripheral blood and immune cell activation in the tumor microenvironment, at baseline and at specified time points during treatment.	During the study treatment
	Biomarker	Gene and/or protein expression of analytes including but not limited to PD-L1, PD-L2, PD-1, or cereblon,	During the study treatment
	Biomarker	The host immune activation status in peripheral blood and tumor at baseline and at specified time points during treatment	
	Biomarker	Baseline genetic/cytogenetic and other molecular biomarkers such as gene expression signatures related to disease or response	
	Biomarker	Measurements of minimal residual disease (MRD)	

Abbreviations: CLL = chronic lymphocytic leukemia; 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-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetic(s).

3. OVERALL STUDY DESIGN

This clinical study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

3.1. Study Design

Study MEDI4736-NHL-001 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 R/R lymphoma or R/R CLL.

The study will consist of 3 parts: dose finding (Phase 1), dose confirmation (Phase 1), and dose expansion (Phase 2). In this study, 4 treatment arms will be investigated:

- Arm A: durvalumab and lenalidomide ± rituximab: **discontinued to the enrollment of new subjects. Subjects already enrolled and treated who are receiving clinical benefit, based on the discretion of the investigator, may continue study treatment after being reconsented.**
- Arm B: durvalumab and ibrutinib
- Arm C: durvalumab and rituximab ± bendamustine
- Arm D: durvalumab (monotherapy)

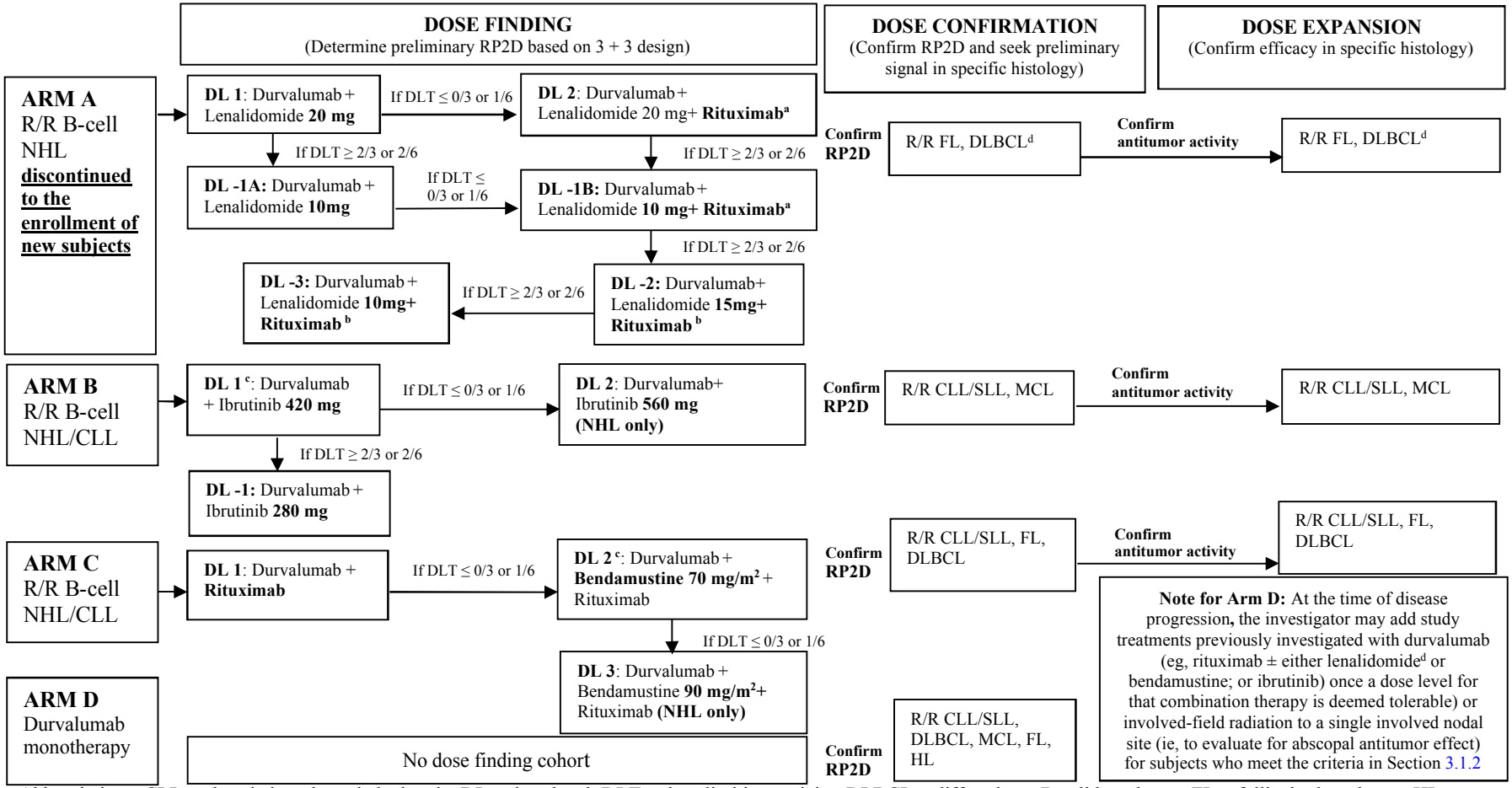
The study will start with 3 dose finding cohorts (Arms A, B, and C) and one dose confirmation cohort (Arm D) in parallel.

All treatment arms will be open for enrollment at study start except in the US, where Arm D will enroll depending on the availability of treatment slots and following the completion of assessment of responses from the combination therapy arms.

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.

Please see Figure 2 for the overall study design and Table 3 for the selected histologies and planned number of subjects in each treatment arm and phase.

Figure 2: 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 DL -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). **Arm A is discontinued to the enrollment of new subjects**. **Only those 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 the dose finding part (Phase 1), a preliminary RP2D will be established for each durvalumab combination treatment using a 3 + 3 design (Storer, 1989). 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 combination will be tested. The durvalumab starting dose is fixed in each of these arms. Three to 6 evaluable subjects will be evaluated in each dose finding cohort; therefore, approximately 15 to 60 (DLT evaluable) subjects with B-cell NHL or CLL are anticipated to be enrolled in the dose finding part. Subjects with CLL/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.

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 (ie, from the first IP dose through completion of Cycle 1 in Arms A, B, and C). 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 (defined in Section 7.2.2). A dose will be considered to be a non tolerated dose (NTD) if ≥ 2 of 3 or 6 evaluable subjects at a dose level experience a DLT. The maximum tolerated dose (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. Non-evaluable subjects may be replaced with another subject at the same dose level.

After full enrollment and completion of the DLT evaluation period of each dose level, the number and type of DLTs and adverse events (AEs) occurring during the DLT evaluation period of that dose level will be assessed by the safety review committee (SRC), which includes the sponsor's medical monitor, drug safety physician, and a subset of investigators who are participating in this clinical study. If a dose level is considered tolerable by the SRC, the SRC may recommend to the sponsor that subsequent dose finding or dose confirmation cohorts may open for enrollment.

During the dose finding part, the decision to evaluate the subsequent dose level for a combination agent, an intermediate dose level, different dosing schedules not currently specified (eg, rituximab dosing Q4W, rituximab dosing in mid-cycle, start of rituximab dosing after Cycle 1, or changes in dose and schedule of other study drugs such as lenalidomide), the need to add additional subjects within any dose cohort, or to declare a dose level as tolerable will be assessed, recommended and documented by the 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.

In the dose confirmation part (Phase 1), once the preliminary RP2D is established, each combination treatment arm will enroll approximately 10 subjects with each prespecified disease

histology (please see Table 3; 7 cohorts of 10 subjects) into Arms A, B, and C to confirm the tolerability and safety of the RP2D and 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. In total, approximately 100 subjects are anticipated to enroll in the dose confirmation part. The Arm D dose confirmation cohort (durvalumab monotherapy) will start at the same time as the dose finding cohorts of the other 4 arms.

In Arm D, at the time of disease progression, if subjects meet the criteria defined in Section 3.1.2, the investigator may add study treatments previously investigated with durvalumab within this protocol (eg, lenalidomide ± rituximab; rituximab ± bendamustine; rituximab; or ibrutinib) once a tolerable dose level is confirmed for that combination (in Arm D it will be permissible for the investigator to add rituximab alone if they consider that it is in the subject's best interest), or the investigator may add local IFRT (please see Section 6.2 for further details). Prior to addition of another therapy to durvalumab, the investigator must consult with the sponsor's medical monitor.

If a promising antitumor signal is detected in any dose confirmation cohort, that cohort will expand and enroll approximately15 additional subjects to further assess the efficacy and to guide the future development of these investigational treatments **in the dose expansion part (Phase 2)**. In total, approximately 105 subjects are anticipated to enroll in the dose expansion part.

All subjects will be evaluated for efficacy on a regular basis as specified in the Section 6.4. 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 concurrent illness) which may result in the need for dose reduction or discontinuation to make recommendations on dose modifications (eg, alternate schedule or dose levels not currently specified) 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 specific disease histology. Each treatment arm may have a separate SRC as appropriate.

The study will also have a global scientific steering committee (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 global scientific steering committee 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 non-clinical data. Please see Section 9.3.2 for the stopping rules defined for the dose confirmation cohorts for efficacy.

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

3.1.1. Potential Pseudoprogression

Atypical responses have been noted with the immune checkpoint inhibitors. These atypical responses are characterized either by the early progression of existing lesions subsequently followed by response, or by the appearance of new lesions, with or without regression of existing tumor lesions (Cheson, 2016).

For subjects in all cohorts and treatment arms, if a subject demonstrates early "tumor progression" (defined as occurring prior to or during Cycle 3 of durvalumab), the investigator is responsible for evaluating whether the subject is experiencing a possible pseudoprogression (ie, tumor flare which is local inflammatory reaction indicating early tumor response at sites of disease such as lymph nodes) which has been described in subjects with solid tumors being treated with durvalumab.

In situations where subjects are experiencing pseudoprogression as assessed by the investigator, subjects may continue the study treatment until a repeat scan, within 12 weeks after initial determination of pseudoprogression, confirms true tumor progression or clinical deterioration, whichever comes earlier. Subjects must be considered likely to tolerate continued treatment and not at risk of serious complications in case of further tumor growth. Please refer to "*Refinement of Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy*" for further guidance (Cheson, 2016).

In situations where subjects are experiencing documented true tumor progression as determined by the investigator, subjects should be discontinued from the study treatment.

3.1.2. Criteria for Adding Combination Agent or Local Involved Field Radiation Therapy to Durvalumab Monotherapy at the time of Progression (Arm D)

For subjects in the durvalumab monotherapy arm (Arm D), at the time of disease progression, the investigator may add study treatments investigated with durvalumab in this protocol (ie, lenalidomide ± rituximab*; bendamustine ± rituximab; rituximab; or ibrutinib) once a dose level of a relevant combination therapy is deemed as tolerable by the SRC, or subjects can receive local involved field radiation therapy (IFRT) to a single involved nodal site (ie, to evaluate for a systemic abscopal antitumor effect).

Subjects with CLL/SLL and RT will not be eligible to receive lenalidomide, and subjects with HL will not be eligible to receive ibrutinib. Decisions about what additional treatment(s) will be added will be made in consultation with the sponsor's medical monitor.

The add-on combination treatment with lenalidomide ± rituximab is no longer allowed.*

For adding a combination agent, a subject must meet the following criteria:

1. Has documented disease progression while on durvalumab monotherapy.
2. Has not received other anticancer/antilymphoma treatments for their disease following progression after durvalumab monotherapy.

3. Does not meet any of the treatment discontinuation criteria in Section 11.1 (except for progressive disease [PD]).
4. Has an absence of rapidly progressing disease or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.
5. Fulfills the laboratory eligibility values defined for specific study treatment (Section 4).
6. Has no prior exposure to new additional IP (ie, lenalidomide, ibrutinib or bendamustine).
7. Has resolution of any AEs from initial therapy (ie, durvalumab monotherapy) to ≤ Grade 1 or baseline.
8. Fulfill other treatment specific eligibility criteria in Section 4 (ie, prior malignancy status, contraception, history or concurrent medical condition or concomitant medication status).

Subjects being considered for IFRT must have:

9. At least 1 measurable lesion (> 1.5 cm) outside of the involved field which will be irradiated.

Subjects who receive local IFRT as additional therapy will continue to follow the Arm D schedule (see Section 6.2).

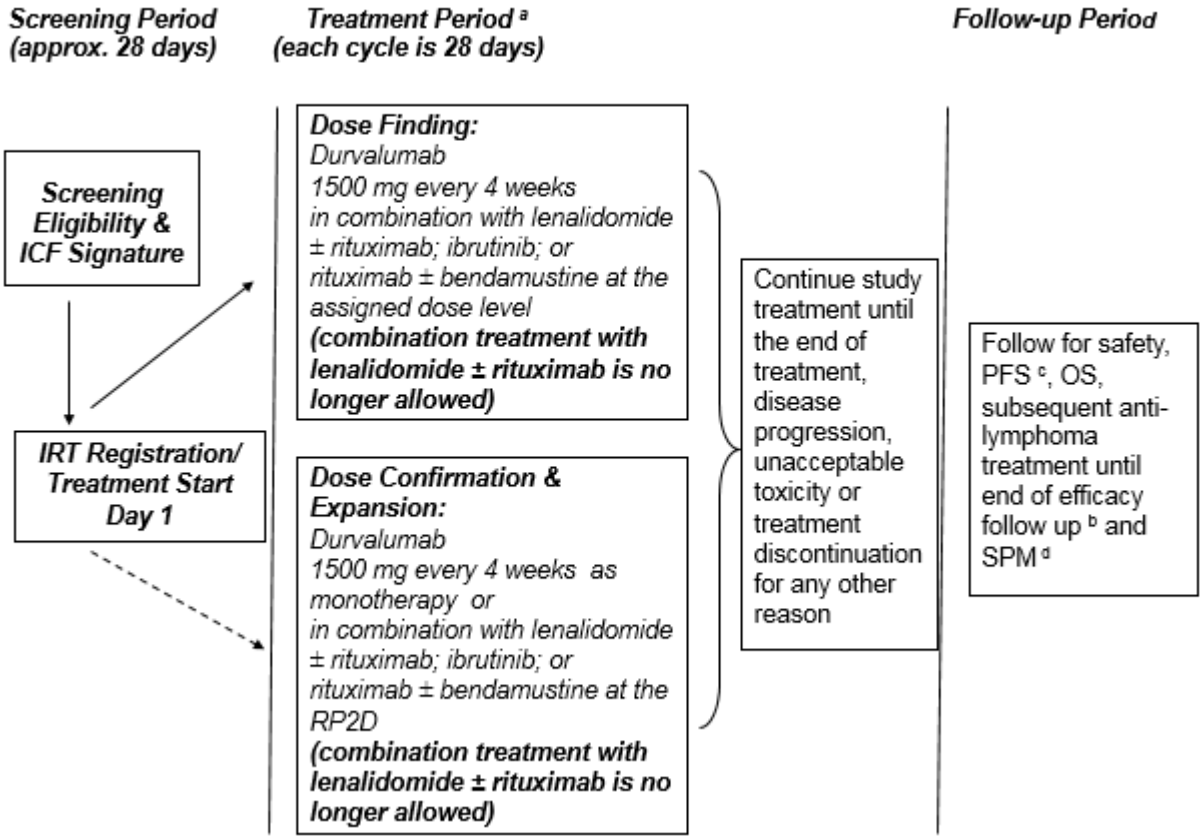
Subjects who receive a combination agent other than local IFRT will follow the visit schedules and assessments specific to each combination agent (eg, the Arm C visit schedule and assessments from Cycle 1 Day 1 will be followed by subjects who receive bendamustine and rituximab in addition to durvalumab) (see Section 6.2). Pharmacokinetic samples for durvalumab will be collected following the addition of a combination agent. No PK samples for lenalidomide or ibrutinib will be collected. Those subjects will be treated according to the treatment schedules described for each arm in Section 7.2 based on the investigator's medical judgment.

3.2. Study Duration for Subjects

The entire study is anticipated to last approximately 6 years. The anticipated study duration for a subject will be up to approximately 3 to 6 years depending on the assigned treatment arm and subject's disease histology.

The study will consist of 3 periods: Screening, Treatment and Follow-up.

Figure 3: Overall Study Flow



Abbreviations: ICF = informed consent form; IRT = interactive response technology; OS = overall survival; RP2D = recommended phase 2 dose; PFS = progression free survival; SPM = second primary malignancy

[a] See Section 7.2 for description of Treatment Administration and Schedule.

[b] All subjects who discontinue treatment and who maintain consent, will proceed directly to the Follow-up Period. This includes subjects who complete the full course of treatment, who discontinue treatment due to progression or toxicity, as well as those who discontinue before progression to pursue a new antilymphoma/CLL therapy.

[c] During the Follow-up Period, efficacy assessments (imaging scans, physical exam, and laboratory tests) will continue at protocol specified time points until first disease progression, start of a new subsequent antilymphoma/CLL therapy, the end of the Efficacy Follow-Up Period, or withdrawal of consent, whichever occurs earlier. Please see Section 6.3.2.

[d] 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.

Arm A is discontinued to the enrollment of new subjects. 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.

3.2.1. Screening Period

The Screening Period will begin once the subject signs the written informed consent form (ICF). All screening assessments must be completed within 28 days prior to Cycle 1 Day 1 (an

exception may be biopsy samples). During this period, the subjects will undergo assessments to determine their eligibility as described in Sections 4, 5, and 6.

Subjects must undergo incisional/excisional/multiple core needle biopsies of their lymphoma in order to evaluate their tumor microenvironments as well as other biomarkers. A formalin-fixed biopsy specimen needs to be collected and submitted to the Central Laboratory during the Screening Period.

An archival lymph node/tumor formalin fixed paraffin embedded (FFPE) sample acquired by a surgical or core needle biopsy within 3 months prior to signing informed consent with no intervening treatment after the biopsy may be acceptable for enrollment of a subject with **poorly accessible tumor following discussion with the sponsor's medical monitor**.

In addition to the screening sample, it is strongly recommended to submit to the Central Laboratory any archival tumor biopsy samples collected prior to study entry (if available) for biomarker analysis.

Subjects who meet the eligibility criteria will be registered in the interactive response technology (IRT) for treatment assignment.

3.2.2. Treatment Period

The Treatment Period begins once the subject receives any IP (ie, durvalumab, lenalidomide, ibrutinib, bendamustine, or rituximab) (Cycle 1 Day 1). Prior to the administration of first dose on Cycle 1 Day 1, the laboratory results must be reviewed by the investigator to reconfirm subject eligibility. If the Central Laboratory results are not available for review yet, then the local laboratory results can be used to reconfirm subject eligibility. Blood samples for laboratories related to safety events must always be collected and submitted to the Central Laboratory according to the schedule in Sections 5 and 6.

Subjects will receive the study treatment (described in Section 7) until the completion of all protocol-specified study treatment, disease progression, unacceptable toxicity, or discontinuation for any other reason.

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.

Arm A is discontinued to the enrollment of new subjects. 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.*

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:

- **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, follicular lymphoma [FL] or marginal zone lymphoma [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.

- **Arm B:** Ibrutinib (PO) continuous, once daily until disease progression, unacceptable toxicity, starts new therapy, or discontinuation for any other reason, ie, subject withdraws consent or discontinues per investigator's discretion.
- **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.
- **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, or subjects can receive involved-field radiation to a single involved nodal site (ie, to evaluate for a systemic abscopal antitumor effect) if they meet the criteria defined in Section 3.1.2. Prior to addition of another therapy to durvalumab, the investigator must consult with the sponsor's medical monitor.

Treatment arms and dose levels for each arm are described and tabulated in Section 7 and 9.3.

Subjects should return to the site as early as possible (within 7 days of last dose or decision for discontinuation) for the End of Treatment Visit assessments if a decision to permanently discontinue study treatment is made, or after completion of the last cycle of treatment.

3.2.3. Follow-up Period

The Follow-up Period will begin at study treatment completion or discontinuation.

Safety Follow-up

All subjects will be followed for 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 SPM for up to 5 years from the last subject's first lenalidomide dose.

Efficacy (Long-Term) Follow-up

The Efficacy Follow-up Period begins upon study treatment completion or discontinuation for each subject. This includes subjects who complete the full course of treatment, who discontinue

treatment due to progression or toxicity, as well as those who discontinue before progression to pursue a new antilymphoma/CLL therapy.

Subjects will be followed for first progression (if applicable), subsequent antilymphoma/CLL therapy, and overall survival according to the schedule described in Section 6.3. Therefore, efficacy assessments as defined in Section 6.3.2 will continue at the protocol-specified time points until first disease progression, withdrawal of consent, the start of a new antilymphoma/CLL therapy, or the end of the Efficacy Follow-up Period. In Arms A (indolent NHL: FL or 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 until their disease progression, whichever date occurs later.

Following completion or discontinuation of durvalumab treatment per protocol for all subjects and completion of the primary analysis (data cutoff date 06 Mar 2019), subjects are no longer required to be followed for disease progression, subsequent antilymphoma/CLL therapy, and overall survival. Follow-up procedures, efficacy assessments, central labs, imaging, and survival data will no longer be collected in the case report forms (CRFs).

In Arm B, subjects receiving benefit from ibrutinib may continue to receive ibrutinib on-study per investigator's medical judgement or discontinue study to receive ibrutinib commercially as standard of care treatment (off-study). Subjects who continue ibrutinib on-study will be treated per investigator's medical judgement and standard of care at the investigative site. The investigator remains responsible to monitor safety, record AEs/SAEs in source documents, and report SAEs to Celgene Drug Safety as stipulated under the full protocol.

3.3. End of Trial

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, and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

This study may enroll approximately 265 subjects globally in regions, including, but not limited to, the United States, Europe, and Japan.

The dose finding part will include the following:

- Arm A: 6 to 30 subjects **(this arm is discontinued to the enrollment of new subjects; subjects already enrolled and treated who are receiving clinical benefit, based on the discretion of the investigator, may continue study treatment after being reconsented)**
- Arm B: 6 to 12 subjects
- Arm C: 3 to 18 subjects

The dose finding part may enroll approximately 15 to 60 (DLT evaluable) subjects; however, the final number of subjects necessary will depend on the number of dose levels studied and number of DLTs observed within each cohort.

The dose confirmation part may enroll approximately 20 subjects in Arm A (2 cohorts of 10 subjects), 20 subjects in Arm B (2 cohorts of 10 subjects), 30 subjects in Arm C (3 cohorts of 10 subjects), and 30 subjects in Arm D (5 cohorts of 5 to 10 subjects) for a total of approximately 100 subjects.

The dose expansion part may enroll approximately 30 subjects in Arm A (2 cohorts of 15 subjects), 30 subjects in Arm B (2 cohorts of 15 subjects) and 45 subjects in Arm C (3 cohorts of 15 subjects) for a total of approximately 105 subjects.

Please see Table 3 for selected histologies and planned number of subjects in each treatment arm and study part, and Table 4 and Table 5 for eligible B-cell NHL or HL histologies.

Table 3: Eligible Histologies per Treatment Arm and Part of the Study

Treatment Arm		Dose Finding		Dose Confirmation[ab]		Dose Expansion[abe]
Arm A[c] (Durvalumab + Lenalidomide ± Rituximab)- **Discontinued to the enrollment of new subjects**	**Dose Finding (RP2D)**	R/R B-cell NHL N = 6-30	**Evaluation of the Safety of RP2D in Specific Histology and Preliminary Signal Seeking**	R/R FL N = 10[d] R/R DLBCL N = 10[d]	**Preliminary Efficacy**	R/R FL N = 15[d] R/R DLBCL N = 15[d]
Arm B (Durvalumab + Ibrutinib)		R/R B-cell NHL/ CLL N = 6-12		R/R CLL/SLL N = 10 R/R MCL N = 10		R/R CLL/SLL N = 15 R/R MCL N = 15
Arm C (Durvalumab + Rituximab ± Bendamustine)		R/R B-cell NHL/ CLL N = 3-18		R/R CLL/SLL N = 10 R/R FL N = 10 R/R DLBCL N = 10		R/R CLL/SLL N =15 R/R FL N = 15 R/R DLBCL N = 15
Arm D (Durvalumab)		No dose finding		R/R CLL/SLL R/R DLBCL R/R FL R/R MCL R/R HL N = 30 (5-10 subjects in each histology)		Not planned

Abbreviations: CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin lymphoma; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; N = number of subjects; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma.

[a] Subjects with FL Grade 3b may be enrolled into DLBCL cohorts but are excluded from FL cohorts.

[b] Subjects with DLBCL not otherwise specified or T-cell/histiocyte rich large B-cell lymphoma will be eligible for the dose confirmation and expansion DLBCL cohorts.

[c] Arm A will exclude subjects with CLL/SLL.

[d] Arm A dose confirmation and dose expansion cohorts are discontinued and will not enroll new subjects.

[e] Celgene decided to not continue with the dose expansion part of the study.

Table 4: Eligible B-cell Non-Hodgkin Lymphoma Histologies (Based on the 2008 WHO Lymphoma Classification) for Phase 1 Dose Finding Cohorts

Eligible B-cell NHL Histologies[a]		
Follicular lymphoma (FL)	Diffuse large B-cell lymphoma (DLBCL), not otherwise specified	Mantle cell lymphoma (MCL)
Chronic lymphocytic leukemia (CLL)	Primary mediastinal (thymic) large B-cell lymphoma (PMBCL)	Nodal marginal zone lymphoma (nMZL)
Small lymphocytic lymphoma (SLL)	ALK-positive large B-cell lymphoma (ALK-positive large BCL)	Splenic marginal zone lymphoma (sMZL)

Table 4: Eligible B-cell Non-Hodgkin Lymphoma Histologies (Based on the 2008 WHO Lymphoma Classification) for Phase 1 Dose Finding Cohorts (Continued)

Eligible B-cell NHL Histologies[a]		
T-cell/histiocyte rich large B-cell lymphoma (T-cell/ histiocyte-rich large BCL)	Transformed lymphoma[b] (TL)	Richter's transformation[b] (RT)

Abbreviations: ALK = anaplastic lymphoma kinase; WHO = World Health Organization.
[a] All histologies listed other than CLL/SLL and MZL are considered as fluorodeoxyglucose (FDG)-avid.
[b] Transformed lymphoma and Richter's transformation will be included but are not part of the 2008 WHO Lymphoma Classification.

Table 5: Eligible Hodgkin Lymphoma Histologies (Based on the 2008 WHO Lymphoma Classification) for Arm D Dose Confirmation Cohort

[a]**Hodgkin Lymphoma Histologies**
Classical Hodgkin lymphoma (cHL)
Nodular sclerosing cHL
Lymphocyte-rich cHL
Mixed cellularity cHL
Lymphocyte-depleted cHL

Abbreviations: WHO = World Health Organization

4.2. Inclusion Criteria

Subjects with R/R lymphoma or CLL requiring therapeutic intervention must satisfy the following criteria to be enrolled in the study:

APPLY to ALL TREATMENT ARMS (Arm A is discontinued to the enrollment of new subjects)

1. Subject is ≥ 18 years of age and ≤ 80 years of age at the time of signing the informed consent form (ICF).

   Exception: At the discretion of the investigator, subjects > 80 years of age may be included if their Eastern Cooperative Oncology Group (ECOG) performance status is ≤ 1; **each** of their individual organ system scores must be ≤ 2 using the Modified Cumulative Illness Rating Scale (CIRS) for comorbidity (Salvi, 2008a; Salvi, 2008b; Appendix I)

2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.

3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.

4. Subject has histologically confirmed and documented eligible histologies as listed in Table 3, Table 4, or Table 5 as assessed by the investigator and local pathologist per the 2008 WHO Lymphoma Classification (Swerdlow, 2008).

   Eligible sub-histologies for the dose confirmation and/or expansion cohorts:

   a. FL cohorts: FL grade 1, 2, and 3a
   b. DLBCL (de novo) cohorts: DLBCL not otherwise specified, T-cell/histiocyte rich large B-cell lymphoma, and FL grade 3b
   c. MCL cohort: MCL
   d. CLL/SLL cohorts: high risk CLL/SLL
   e. HL cohort: cHL, nodular sclerosing cHL, lymphocyte-rich cHL, mixed cellularity cHL, lymphocyte-depleted cHL

5. Subject has been previously treated with at least one prior systemic chemotherapy, immunotherapy, or chemoimmunotherapy.
   Note: Local involved field radiation therapy (IFRT) or antibiotic-based therapy is **not deemed as systemic therapy** for this study.

6. Subject with high-risk CLL/SLL is defined by the presence of at least one of the following factors:

   a. Complex karyotype;
   b. del (17p) abnormality;
   c. Mutated TP53;
   d. Ibrutinib or other BTK-inhibitor failure (defined as progression while on ibrutinib treatment [excluding isolated early lymphocytosis]; or an inadequate tumor response which is less than partial response [PR] [Hallek, 2008; Cheson, 2014]);
   e. Relapsed/progressive disease within 6 months of completing their last therapy which may include investigational drug.

7. Subject is willing and able to undergo biopsy:

   a. Subject with lymphoma is willing and able to undergo tumor/lymph node biopsy (incisional/excisional or multiple core needle)
      - During the Screening Period,
      - Any time during Cycle 2 (strongly recommended), and
      - At the time of disease progression from subjects who have achieved objective response (CR/PR) to study treatment.
   b. Subject with CLL is willing and able to undergo bone marrow biopsy during the Screening and Treatment Periods.

   Material from a fine needle aspiration **is not acceptable.**

8. Subject who has documented active relapsed or refractory disease **requiring** therapeutic intervention.

9. Subject who has measurable disease:

a. For subject with lymphoma, bi-dimensionally measurable disease on cross-sectional imaging by computed tomography (CT) with at least one nodal or extranodal lesion ≥ 2.0 cm in its longest dimension.
Note: A previously irradiated lesion is ineligible to be used as a measurable target lesion.
b. For subject with CLL, in need of treatment as defined by IWCLL Guidelines for the Diagnosis and Treatment of CLL (Appendix H).

10. Subject who has performance status of 0, 1, or 2 on the ECOG scale.
11. Subject who has life expectancy of greater than 6 months.
12. Subject who fulfills the following laboratory requirements:

Table 6: Eligible Laboratory Values

Laboratory Value/ Treatment Arms	**Arm A**	**Arm B**	**Arm C**	**Arm D**
ANC (cells/mm^3)	≥ 1500	≥ 1000		
	Subjects with ANC ≥ 500 (cells/mm^3) may be allowed **in the dose confirmation and expansion cohorts only if neutropenia is secondary to bone marrow involvement documented** as ≥ 80% bone marrow infiltration of CLL cells or ≥ 50% bone marrow infiltration of lymphoma cells by pretreatment bone marrow biopsy following the discussion with the sponsor's medical monitor. These subjects should not have any evidence of active bacterial infection within 14 days of Cycle 1 Day 1 (ie, off of oral and IV antibiotics for at least for 14 days). **These subjects will be excluded from the dose finding cohorts.**			
Platelets (cells/mm^3)	≥ 75,000			
	Subjects with platelets ≥ 20,000 cells/mm^3 may be allowed **in the dose confirmation and expansion cohorts only if thrombocytopenia is secondary to bone marrow involvement documented** as ≥ 80% bone marrow infiltration of CLL cells or ≥ 50% bone marrow infiltration of lymphoma cells by pretreatment bone marrow biopsy following the discussion with the sponsor's medical monitor. These subjects should not have any evidence of active bleeding or clinically significant coagulopathy. **These subjects will be excluded from the dose finding cohorts.**			
AST/ALT (ULN)	≤ 2.5 × ULN			
	In the case of liver involvement by lymphoma, subjects with AST/ALT ≤ 5.0 × ULN may be allowed **in the dose confirmation and expansion cohorts only following the discussion with the sponsor's medical monitor.** **These subjects will be excluded from the dose finding cohorts.**			

Table 6: Eligible Laboratory Values (Continued)

Laboratory Value/ Treatment Arms	Arm A	Arm B	Arm C	Arm D
Total Bilirubin (serum) (ULN)	≤ 1.5 × ULN			
	In the case of Gilbert's Syndrome, or documented liver or pancreatic involvement by lymphoma, subjects with total bilirubin ≤ 3.0 mg/dL may be allowed **in the dose confirmation and expansion cohorts only following the discussion with the sponsor's medical monitor.** **These subjects will be excluded from the dose finding cohorts.**			
Creatinine Clearance (mL/min) based on Cockcroft-Gault formula	≥ 60 (eligible for all parts) **≥ 40 (ineligible for dose finding cohorts of Arm A)**	≥ 40		
PT/INR (ULN)	--	< 1.5 × ULN	--	--
PTT/aPTT (ULN)	--	< 1.5 × ULN	--	--

Abbreviations: ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST/ALT = aspartate transaminase / aspartate transaminase; CLL = chronic lymphocytic leukemia; INR = international normalized ratio; LLN = lower limit of normal; NHL = non-Hodgkin lymphoma; PTT = partial thromboplastin time; ULN = upper limit of normal.

13. Female subject of childbearing potential (FCBP[1]) who is sexually active with a male must:
    a. Have 2 negative pregnancy tests as verified by the investigator prior to starting any IP therapy. They must agree to ongoing pregnancy testing during the course of the study, and after the last dose of any IP. This applies even if the subject practices true abstinence[2] from heterosexual contact.
    b. Use effective methods (1 highly effective and 1 additional effective [barrier] method) of contraception from 28 days prior to starting durvalumab, and must agree to continue using such precautions while taking durvalumab (including dose interruptions) and for 90 days after the last dose of durvalumab. Cessation of contraception after this point should be discussed with a responsible physician.

[1] A female subject of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

[2] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods (defined as one that results in a low failure rate [ie, less than 1% per year] when used consistently and correctly):

  (i) Intrauterine device (IUD). See Section Section 8.2 Prohibited Concomitant Medications and Procedures.

  (ii) Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [eg, desogestrel]).

  (iii) Tubal ligation

  (iv) Partner's vasectomy

- Additional effective methods:

  (i) Male condom

  (ii) Diaphragm

  (iii) Cervical cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

c. Agree to abstain from breastfeeding during study participation and for at least 90 days after the last dose of durvalumab.
d. Refrain from egg cell donation while taking durvalumab and for at least 90 days after the last dose of durvalumab.

14. Male subject who is sexually active with a female partner of childbearing potential must:

a. Use male condom plus spermicide (even if he has undergone a successful vasectomy) from starting dose of durvalumab (Cycle 1 Day 1) through 90 days after receipt of the last dose of durvalumab. True abstinence is acceptable only when this is in line with the preferred and usual lifestyle of nonsterilized male subject.
b. Refrain from semen or sperm donation while taking durvalumab and for at least 90 days after the last dose of durvalumab.

Inclusion numbers 15-17 APPLY to ARM A only:

15. Female subject of childbearing potential must:

a. Have 2 negative pregnancy tests as verified by the investigator prior to starting any IP therapy (ie, durvalumab, lenalidomide and rituximab). They must agree to ongoing pregnancy testing during the course of the study, and after last dose of any IP. This applies even if the subject practices true abstinence from heterosexual contact.
b. Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective (1 highly effective and 1 additional effective method) contraception without interruption, 28 days prior to starting any IP, during the IP therapy (including dose interruptions), and

for 12 months after the last dose of rituximab, 90 days after the last dose of durvalumab, or 28 days after the last dose of lenalidomide, whichever is longer.

c. Agree to abstain from breastfeeding during study participation and for at least 28 days after the last dose of lenalidomide or 12 months after the last dose of rituximab, whichever is longer.

d. Refrain from egg cell donation while taking durvalumab and for 90 days after the last dose of durvalumab.

16. Male subject must:

a. Practice true abstinence or agree to use a condom during sexual contact with a pregnant female or an FCBP while participating in the study, during dose interruptions and for at least 28 days after the last dose of lenalidomide, or for at least 90 days after the last dose of durvalumab, even if he has undergone a successful vasectomy, whichever is longer.

b. Agree to not donate semen or sperm during the IP therapy and for 28 days after the last dose of lenalidomide or 90 days after the last dose of durvalumab, whichever is longer.

17. All subjects must:

a. Have an understanding that lenalidomide could have a potential teratogenic risk.

b. Agree to abstain from donating blood while taking lenalidomide therapy and for 28 days after the last dose of lenalidomide therapy or 90 days after the last dose of durvalumab, whichever is longer.

c. Agree not to share lenalidomide with another person.

d. Agree to be counseled about pregnancy precautions and risk of fetal exposure.

Inclusion numbers 18-19 APPLY to ARM B only:

18. Female subject of childbearing potential must:

a. Have 2 negative pregnancy tests as verified by the investigator prior to starting any IP therapy (ie, durvalumab and ibrutinib). They must agree to ongoing pregnancy testing during the course of the study, and after last dose of any IP. This applies even if the subject practices true abstinence from heterosexual contact.

b. Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective (1 highly effective and 1 additional effective method) contraception without interruption, 28 days prior to starting IP therapy, during the IP therapy (including dose interruptions) and for 90 days after the last dose of IP.

c. Agree to abstain from breastfeeding during study participation and for at least 90 days after last dose of IP therapy.

d. Refrain from egg cell donation while taking durvalumab and for 90 days after the last dose of durvalumab.

19. Male subject must:

a. Practice true abstinence or agree to use a condom during sexual contact with a pregnant female or an FCBP while participating in the study, during dose

interruptions and for at least 90 days following the last dose of IP, even if he has undergone a successful vasectomy, whichever is longer.

b. Agree to not donate semen or sperm during the IP therapy and for 28 days after the last dose of ibrutinib or 90 days after the last dose of durvalumab, whichever is longer.

Inclusion numbers 20-21 APPLY to ARM C only:

20. Female subject of childbearing potential must:

a. Have 2 negative pregnancy tests as verified by the investigator prior to starting any IP therapy (ie, durvalumab, bendamustine and rituximab). They must agree to ongoing pregnancy testing during the course of the study, and after last dose of any IP. This applies even if the subject practices true abstinence from heterosexual contact.

b. Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective (1 highly effective and 1 additional effective method) contraception without interruption, 28 days prior to starting IP therapy, during the IP therapy (including dose interruptions) and for 12 months after the last dose of rituximab or for 90 days after the last dose of the other IP (ie, bendamustine and/or durvalumab) dose, whichever is longer.

c. Agree to abstain from breastfeeding during study participation and for at least 12 months after the last dose of rituximab.

d. Refrain from egg cell donation while taking durvalumab and for 90 days after the last dose of durvalumab.

21. Male subject must:

a. Practice true abstinence or agree to use a condom during sexual contact with a pregnant female subject or an FCBP while participating in the study, during dose interruptions and for at least 90 days after the last dose of durvalumab or 6 months after the last dose of bendamustine, even if he has undergone a successful vasectomy, whichever is longer.

b. Agree to not donate semen or sperm during the IP therapy and for at least 90 days after the last dose of durvalumab or 6 months after the last dose of bendamustine, whichever is longer.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

APPLY to ALL TREATMENT ARMS (Arm A is discontinued to the enrollment of new subjects)

1. Subject who has known or suspected central nervous system (CNS) or meningeal involvement by lymphoma.
2. Subject who has other lymphoma histologies which are not listed on Table 3, Table 4, Table 5 (eg, human immunodeficiency virus [HIV]-associated lymphomas, CNS lymphoma, Waldenstrom's macroglobulinemia).

a. Subject has blastoid variants of MCL or MCL with blastoid transformation.

b. Dose Confirmation and/or Expansion Parts only:
   - Transformed lymphoma or Richter's transformation
   - DLBCL histology other than: not otherwise specified or T-cell/histiocyte rich

3. Subject who has any histopathologic finding consistent with myelodysplastic syndrome on bone marrow studies.
4. Subject who has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
5. Subject who has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
6. Subject who has any condition that confounds the ability to interpret data from the study.
7. Subject who has any uncontrolled inter-current illness including, but not limited to, ongoing or active infection, current pneumonitis, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from durvalumab and/or other investigational treatment regimens, or compromise the ability of the subject to give written informed consent.
8. Subject who is concurrently enrolled in another clinical study, unless in a follow-up period or it is an observational study.
9. Subject who has any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment.

   Note: Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.

10. Subject who has received:

    a. Any systemic antilymphoma/leukemia therapy, or hematopoietic growth factors, blood or platelets transfusions within 14 days prior to the first dose of IP (ie, Cycle 1 Day 1) and/or
    b. Any radioimmunotherapy within 3 months prior to the first dose of IP (ie, Cycle 1 Day 1).

    Exception: The use of hematopoietic growth factors or blood product transfusional support for subjects with extensive marrow involvement by lymphoma or CLL may be allowed during the Screening Period after consultation with the sponsor's medical monitor **in the dose confirmation and expansion cohorts only** (see Table 6).

11. Subject who has unresolved toxicities from prior anticancer therapy, defined as having not resolved to NCI CTCAE v4.03 ≤ Grade 1 with the exception of alopecia and laboratory values listed per the exclusion criteria. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by durvalumab or other investigational treatments may be included (eg, hearing loss) after consultation with the sponsor's medical monitor.

12. Subject who received any prior mAb against PD-1 or PD-L1 and/or any prior:
    a. **Arm A only:** IMiDs (eg, lenalidomide, thalidomide);
    b. **Arm B only:** ibrutinib or other BTK inhibitor;
    c. **Arms C only:** bendamustine (except dose level 1).
13. Subject who has history of organ transplant or allogeneic hematopoietic stem cell transplantation.
14. Subject who has taken corticosteroids during the last week prior to the first dose of IP (ie, Cycle 1 Day 1), unless administered at a dose equivalent to ≤ 10 mg/day prednisone.

    Exception: For subjects with bulky disease, systemic symptoms, compressive disease, or rapidly progressing adenopathies, pre-phase treatment with 1 mg/kg/day prednisone, or equivalent, for a maximum of 7 days is permitted prior to Cycle 1 Day 1, at the discretion of the investigator. A washout period does not apply.
15. Subject who has received live, attenuated vaccine within 30 days prior to the first dose of durvalumab (Note: Subjects, if enrolled, should not receive live vaccine during the study and for 12 months after last dose of rituximab or until recovery of B-cells and for 120 days after the last dose of durvalumab, whichever is longer).
16. Subject who has undergone major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of the IP (ie, Cycle 1 Day 1) or still recovering from prior surgery.
17. Subject who has active documented autoimmune disease (including, but not limited to, inflammatory bowel disease, celiac disease, Wegener syndrome, hemolytic anemia, or immune thrombocytopenic purpura) prior to first dose of durvalumab.

    Exception: Type 1 diabetes mellitus and hypothyroidism which are well controlled
18. Subject who has history of primary immunodeficiency or tuberculosis.
19. Subject who has known seropositivity for or active infection for human immunodeficiency virus (HIV) or hepatitis C virus (HCV).
20. Subject who is seropositive for or active viral infection with hepatitis B virus (HBV)
    a. HBV surface antigen (HBsAg) positive
    b. HBV surface antigen (HBsAg) negative, HBV core antibody (anti-HBc) positive, and detectable viral DNA

    Note:
    A subject who is seropositive for anti-HBs because of prior exposure or vaccination (anti-HBc and HBsAg negative) will be eligible. In this case, viral DNA does not need to be tested).
21. Female subject who is pregnant, breastfeeding, or intend to become pregnant during the participation in the study.
22. Subject who has other invasive malignancy within 2 years prior to signing the ICF except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin, ductal carcinoma in situ of the breast, or incidental histologic

finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) that has/have been surgically cured.

a. **Arm A only:** Subject who has history of other malignancies, unless the subject has been free of the disease for ≥ 5 years prior to signing the ICF.
Exceptions: History of previously treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin and related localized non-melanoma skin cancer, carcinoma in situ of the cervix, carcinoma in situ of breast, incidental histologic finding of prostate cancer (T1a or T1b using the TNM clinical staging system).

23. Subject who has known allergy or hypersensitivity to the active substance or any of the excipients, or to other humanized mAbs.

Exclusion numbers 24-26 APPLY to ARM A only:

24. Subjects with CLL or SLL.
25. Subject who has peripheral neuropathy Grade 3 or 4.
26. Subject who is at risk for a thromboembolic event and is not willing to take prophylactic treatment.

Exclusion numbers 27-28 APPLY ARMS A and C only (if subject will receive rituximab):

27. Subject who does not have CD20 positive lymphoma or CLL.
28. Subject who has hypersensitivity to rituximab.

Exclusion numbers 29-32 APPLY to ARM B only:

29. Subject who has transfusion-dependent thrombocytopenia or a history of bleeding disorders or clinical conditions (eg, gastrointestinal bleeding or constitutional disorders) that may increase the risk of life-threatening bleeding when thrombocytopenic.
30. Subject who has history of stroke or intracranial hemorrhage within 6 months prior to signing the ICF.
31. Subject who receives the medications that are strong inhibitors or inducers of CYP3A (eg, itraconazole, ketoconazole, clarithromycin, ritonavir, phenytoin, pentobarbital, and rifampin) and cannot change.
32. Subject who has received concomitant anticoagulation with warfarin or other vitamin K antagonists within 7 days prior to signing the ICF and cannot change. The use of other anticoagulants (eg, heparins) and antiplatelet agents is allowed per investigator's discretion. Investigator questions regarding this should be addressed to the sponsor's medical monitor or the study country principal investigators.

Exclusion number 33 APPLIES to ARM C only (if subject will receive bendamustine):

33. Subject who should concurrently use allopurinol, eg, because of gout, and unwilling to switch to another equivalent medication. (Subjects with gout are advised to switch to another antigout medication, because of the risk of Stevens-Johnson syndrome observed in subjects using bendamustine and allopurinol).

5. TABLE OF EVENTS

Table 7: Table of Events – Arm A - Durvalumab and Lenalidomide ± Rituximab

(This arm is discontinued to enrollment of new subjects; the procedures apply to continuing subjects in the study.)

Events	Screening Period	Treatment Period													Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT[a]	
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28/ D90	Efficacy[b] /SPM
Informed Consent	X																
IRT Registration	X	X		X	X		X		X		X	X	X	X	X		
Inclusion/Exclusion Criteria	X																
Demographics	X																
Medical History & Disease History	X																
Prior Anticancer Therapy	X																
Physical Examination & B Symptoms	X	X			X		X		X		X	X	X	X	X	X	X (until PD)
Height	X																
Weight	X	X			X		X		X		X	X	X	X	X		
Body Surface Area	X	X															
Vital Sign Monitoring[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X			X		X		X		X	X	X	X	X		
CIRS (only subjects > 80 years)	X																

Table 7: Table of Events – Arm A - Durvalumab and Lenalidomide ± Rituximab (Continued)

Events	Screening Period	Treatment Period														Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT [a]		
	D -28 to -1	D1	D2&D 3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28 /D90	Efficacy /SPM[b]
12-lead ECG	X												X				
HBV Screening	X																
CBC & Differential	X	X	X (C1D3 only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X (until PD)
Clinical Chemistry (including LDH)	X	X	X (C1D3 only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X (until PD)
GGT, Amylase, Lipase	X	X		X	X	X	X	X	X	X	X	X	X				
Thyroid Function Tests[d]	X	X		X (C1D15 only)	X	X	X	X	X	X		X (C6, C8, C10, C12 only)	X			X (D90 only)	
Calculated Creatinine Clearance (serum)	X																
Coagulation	X	X		X (C1D15 only)	X		X		X		X	X	X			X (D90 only)	
Quantitative Immunoglobulins	X												X				
Urinalysis	X												X				

Table 7: Table of Events – Arm A - Durvalumab and Lenalidomide ± Rituximab (Continued)

Events	Screening Period	Treatment Period														Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT [a]		
	D -28 to -1	D1	D2&D 3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28 /D90	Efficacy /SPM [b]
Pregnancy Counseling	X	X			X		X		X		X	X	X	X	X	X	
Pregnancy Test - for FCBP with Regular or No Menstrual Cycles	X Once -10 to -14 days	X Within 24 hours of C1D1		X	X		X		X		X	X	X	X	X	28 days after last lenalidomide dose & D90	
Pregnancy Test- for FCBP with Irregular Menstrual Cycles	X Once -10 to -14 days	X Within 24 hours of C1D1		X	X	X	X	X	X	X	Every cycle Days 1 and 15				X	Both 14 & 28 days after last lenalidomide dose & D90	
Efficacy Response Assessment									X			X (C7 & C10)	X	Every 6 cycles/months up to PD or start of a new antilymphoma therapy			

Table 7: Table of Events – Arm A - Durvalumab and Lenalidomide ± Rituximab (Continued)

Events	Screening Period	Treatment Period														Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT [a]		
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28 /D90	Efficacy /SPM [b]
CT Scans (Neck, Chest, Abdomen &Pelvis) (contrast-enhanced unless contraindicated) **(Lymphoma)**	X								X			X (C7 & C10)	X	Every 6 cycles/months up to PD or start of a new antilymphoma treatment [e]			
FDG-PET-CT **(FDG-avid Lymphoma)**	X (strongly recommended)	To confirm CR by CT scan alone at any time during the study (within 14 days following demonstration of nodal CR by CT scan alone)															
Bone Marrow Biopsy & Aspirate **(Lymphoma)**	X [f]	To confirm true CR (within 28 days of meeting the criteria for nodal CR by CT scan alone) except in subjects with no evidence of lymphomatous marrow involvement at baseline [g]															
MRD Assessment – Whole Blood **(in subjects with MCL and FL)[h]**		X							Within 28 days of meeting the criteria for PET negative CR and then every 3 cycles while on treatment or every 6 months in follow-up until evidence of clinical PD [h]								
MRD Assessment – Bone Marrow Aspirate **(in subjects with FL and MCL)[h]**									Within 28 days of meeting the criteria for PET negative CR and then every 3 cycles while on treatment or every 6 months in follow-up (as available) [h]								
PK- Blood Sampling [i] for Durvalumab		X	X	X	X	X			X			X (C6 & C10)	X				
PK- Blood Sampling [j] for Lenalidomide		X	X (D2 only)	X (D15 only)													

Table 7: Table of Events – Arm A - Durvalumab and Lenalidomide ± Rituximab (Continued)

Events	Screening Period	Treatment Period														Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT [a]		
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28 /D90	Efficacy /SPM[b]
Immunogenicity (ADA)- Blood Sample[k]		X			X				X			X (C6 & C10)	X				
Biomarker- Saliva (pharmacogenomics)	X																
Biomarker- PBMC Isolation	X					X				X			X				
Biomarker-Whole Blood for Immunophenotyping	X	X		X (D8 & D15 only)	X	X											
Biomarker-Serum	X	X			X												
Biomarker-Plasma (Cytokines/Soluble Factors)	X	X			X	X		X		X			X				
Biomarker-Tumor Biopsy[l] **(Lymphoma)**	X[m]				X (recommended)		At the time of disease progression (within 14 days) in subjects who achieved objective responses (CR/PR)										
Biomarker- Bone Marrow Biopsy[n] &Aspirate **(Lymphoma)**	X	**If available**, bone marrow biopsy samples will be submitted to the Central Laboratory for biomarker analysis at any time performed (such as at the time of nodal CR by CT alone).															
Durvalumab IV Infusion		X			X		X		X		X	X					
Rituximab IV Infusion Schedule 1 (DL-1B & DL2)			X (D2)	X Weekly	X		X		X		X						

Table 7: Table of Events – Arm A - Durvalumab and Lenalidomide ± Rituximab (Continued)

Events	Screening Period	Treatment Period														Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT [a]		
	D -28 to -1	D1	D2& D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28 /D90	Efficacy /SPM[b]
Rituximab IV Infusion Schedule 2 (DL-2 & DL-3)			X (D2)		X		X		X		X	X (C6, C7 & C8)					
Dispense Lenalidomide (PO) **(in FL or MZL)**		X			X		X		X		X	X					
Dispense Lenalidomide (PO) **(in aggressive histologies)**		X			X		X		X		X	X	X	X			
Drug Accountability		X		X	X		X		X		X	X	X	X	X		
Tumor Lysis Prophylaxis (Allopurinol or equivalent)- **recommended**		X	X	X													
Concomitant Medications/ Procedures	After signing informed consent through 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later.																
Adverse Events (AE)	After signing informed consent through 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later.																
Subsequent Antilymphoma/Anticancer Treatment Status	After signing informed consent until the subject dies, withdraws consent from the study, or for up to: – 24 months from the date of his/her last dose (in FL or MZL) or – 24 months after his/her last durvalumab dose or disease progression, whichever date occurs later (in aggressive histologies).																
Survival Status																	
Second Primary Malignancy (SPM) Assessment	After signing informed consent until the subject dies, withdraws consent from the study or for up to 5 years from the date of last subject's first lenalidomide dose (including SPM follow-up 90 days after the last dose of durvalumab).																

Abbreviations: ADA = anti-drug antibodies; BMB = bone marrow biopsy; C = cycle; CBC = complete blood count; CIRS = cumulative illness rating scale; CR = complete response; CT = computed tomography; D = day; DL = dose level; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram ; ECOG= Eastern Cooperative Oncology Group; EOT = end of treatment; EOT-D = end of durvalumab treatment; FCBP = female of childbearing potential; FDG = fluorodeoxyglucose; FDG-PET = fluorodeoxyglucose-positron emission tomography; FL = follicular lymphoma; fT3 = free triiodothronine; fT4 = free thyroxine; GGT = gamma glutamyl transferase; HBV = hepatitis B virus; HL = Hodgkin lymphoma; IRT = integrated response technology; IV = intravenous; LDH = lactic dehydrogenase; MCL = mantle cell lymphoma; MRD = minimal residual disease; MZL = marginal zone lymphoma; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PK = pharmacokinetics; PO = orally; PR = partial response; PS = performance status; SPM = second primary malignancy.

[a] For subjects with indolent lymphoma, the EOT for all study treatments and the EOT-D will be the same visit unless subjects discontinue durvalumab treatment (earlier than Cycle 13) due to toxicity.

[b] Efficacy Follow-up will be performed (a) up to 24 months from subject's last durvalumab dose (in FL or MZL) or (b) up to 24 months from subject's last durvalumab dose or disease progression, whichever occurs later (in aggressive histologies). Following completion or discontinuation of durvalumab treatment per protocol for all subjects and completion of the primary analysis (data cutoff date 06 Mar 2019), subjects are no longer required to be followed for disease progression, subsequent antilymphoma/CLL therapy, and overall survival. Follow-up procedures, efficacy assessments, central labs, imaging, and survival data will no longer be collected in the CRFs.

[c] Subjects will have their blood pressure, pulse and body temperature measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (within an hour prior to start of durvalumab administration);
- At 30 minutes during the infusion (± 5 minutes);
- At the end of the infusion (at 60 minutes ± 5 minutes);
- In the 2-hour observation period post-infusion: every 30 minutes after the infusion (ie, 90, 120, 150, and 180 minutes from the start of the infusion) (± 5 minutes) – **for the first infusion only and then for subsequent infusions as clinically indicated**.
- If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated.

[d] Thyroid stimulating hormone (TSH), fT4, and fT3. Cycle 6 onward: TSH only, if TSH is abnormal, then reflex testing for fT4 and fT3.

[e] Once a subject has experienced confirmed progression, or started a new antilymphoma therapy, no further scans, physicial examination, or laboratory assessments are required.

[f] Screening bone marrow biopsy is required in subjects with suspected bone marrow involvement by lymphoma per investigator's discretion.

[g] If an FDG-PET-CT is performed and confirms FDG-negative CR, BMB and aspirate are not required for subjects with aggressive histologies (eg, DLBCL and HL).

[h] Please see Section Section 6.4.1.4 for MRD assessments.

[i] Please see Section Section 6.6.1 for PK sample collection time points for durvalumab.

[j] Please see Section Section 6.6.2 for PK sample collection time points for lenalidomide.

[k] Please see Section 6.7 for immunogenicity sample collection time points.

[l] In addition, it is strongly recommended to submit to the Central Laboratory any archival lymph node/tumor biopsy samples collected prior to study entry as well as any biopsy sample collected during the study for biomarker analysis.

[m] The only exception is that an archival diagnostic lymph node/tumor formalin-fixed paraffin-embedded (FFPE) biopsy acquired by a surgical or core needle biopsy within 3 months and with no intervening treatment prior to signing informed consent may be acceptable for enrollment in subjects with poorly accessible tumor following the discussion with the sponsor's medical monitor.

[n] In addition, it is strongly recommended to submit to the Central Laboratory any archival bone marrow biopsy samples collected prior to study entry as well as any biopsy samples collected during the study for biomarker analysis.

Detailed information (including visit windows) for each assessment is provided in Section 6.

Table 8: Table of Events – Arm B - Durvalumab and Ibrutinib

Events	Screening Period	Treatment Period														Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT		
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28 /D90	Efficacy[a]
Informed Consent	X																
IRT Registration	X	X			X		X		X		X	X	X	X	X		
Inclusion/Exclusion Criteria	X																
Demographics	X																
Medical History & Disease History	X																
Prior Anticancer Therapy	X																
Physical Examination & B symptoms	X	X			X		X		X		X	X	X	X	X	X	X (until PD)
Height	X																
Weight	X	X			X		X		X		X	X	X	X	X		
Vital Sign Monitoring[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X			X		X		X		X	X	X	X	X		
CIRS (only subjects > 80 years)	X																
12-lead ECG	X												X				
HBV Screening	X																

Table 8: Table of Events – Arm B - Durvalumab and Ibrutinib (Continued)

Events	Screening Period	Treatment Period														Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT		
	D -28 to -1	D1	D2&D 3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28 /D90	Efficacy[a]
CBC & Differential	X	X	X (D3 only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X (until PD)
Clinical Chemistry (including LDH)	X	X	X (D3 only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X (until PD)
GGT, Amylase, Lipase	X	X		X	X	X	X	X	X	X	X	X	X				
Thyroid Function Tests[c]	X	X		X (D15 only)	X	X	X	X	X	X		X (C6, C8, C10, C12 only)	X			X (D90 only)	
Calculated Creatinine Clearance (serum)	X																
Coagulation	X	X		X (D15 only)	X		X		X		X	X	X			X (D90 only)	
Direct Antiglobulin-Blood **(CLL only)**[d]	X																
Quantitative Immunoglobulins	X												X				
Urinalysis	X												X				
Pregnancy Test for FCBP	X	X			X		X		X		X	X	X	X	X	X	

Table 8: Table of Events – Arm B - Durvalumab and Ibrutinib (Continued)

Events	Screening Period	Treatment Period													Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT	
	D -28 to -1	D1	D2& D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28 /D90	Efficacy[a]
Efficacy Response Assessment									X			X (C7 & C10)	X	Every 6 cycles/months up to PD or start of a new antilymphoma/CLL therapy			
CT Scans (Neck, Chest, Abdomen &Pelvis) (contrast-enhanced unless contraindicated) **(Lymphoma)**	X								X			X (C7 & C10)	X	Every 6 cycles/months up to PD or start of a new antilymphoma/CLL therapy[e]			
FDG-PET-CT **(FDG-avid Lymphoma)**	X (strongly recommended)	To confirm CR by CT scan alone at any time during the study (within 14 days following demonstration of nodal CR by CT scan alone)															
Bone Marrow Biopsy & Aspirate **(Lymphoma)**	X[f]	To confirm true CR (within 28 days of meeting the criteria for nodal CR by CT scan alone) except in subjects with no evidence of lymphomatous marrow involvement at baseline[g]															
MRD Assessment-Whole Blood **(in subjects[h] with MCL and FL)**		X							Within 28 days of meeting the criteria for PET negative CR and then every 3 cycles while on treatment or every 6 months in follow-up until evidence of clinical PD[h]							
MRD Assessment-Bone Marrow Aspirate **(in subjects with MCL and FL)**[h]									Within 28 days of meeting the criteria for PET negative CR and then every 3 cycles while on treatment or every 6 months in follow-up (as available)[h]							

Table 8: Table of Events – Arm B - Durvalumab and Ibrutinib (Continued)

Events	Screening Period	Treatment Period														Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT		
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28 /D90	Efficacy[a]
CT Scans (Neck, Chest, Abdomen & Pelvis) (contrast-enhanced unless contraindicated) **(CLL)**[i]	X											X[j] (C7)					
Bone Marrow Biopsy & Aspirate[k] **(CLL)**	X											X (C7)	X				
MRD Assessment – Whole Blood **(in subjects with CLL)**[l]		X							Within 14 days of meeting the criteria for suspected CR by clinical, CBC-based, and imaging assessments and then every 3 cycles while on treatment or every 6 months in follow-up til evidence of clinical PD[l]								
MRD Assessment – Bone Marrow Aspirate **(in subjects with CLL)**[l]									Within 12 weeks of meeting the criteria for suspected CR by clinical, CBC-based, and imaging assessments and then every 3 cycles while on treatment or every 6 months in follow-up til evidence of clinical PD (as available)[l]								
PK- Blood Sampling for Durvalumab[m]		X	X	X	X	X			X			X C6 & C10)	X				
PK- Blood Sampling for Ibrutinib[n]		X	X (D2 only)	X (D15 only)													
Immunogenicity (ADA)-Blood Sample[o]		X			X				X			X (C6 & C10)	X				

Table 8: Table of Events – Arm B - Durvalumab and Ibrutinib (Continued)

Events	**Screening Period**	**Treatment Period**													**Follow-up**	
		C1			**C2**		**C3**		**C4**		**C5**	**C6-13**	**C14/ EOT-D**	**≥ C15**	**EOT**	
	D -28 to -1	**D1**	**D2&D 3**	**D8, D15 & D22**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**		**Safety D28 /D90**	**Efficacy[a]**
Biomarker- Saliva (pharmacogenomics)	X																
Biomarker- PBMC Isolation	X					X				X			X				
Biomarker-Whole Blood for Immunophenotyping	X	X		X (D8 & D15 only)	X	X											
Biomarker-Serum	X	X			X												
Biomarker-Plasma (Cytokines/Soluble Factors)	X	X			X	X		X		X			X				
Biomarker-Tumor Biopsy[p] **(Lymphoma)**	X[q]				X (recommended)		At the time of disease progression (within 14 days) in subjects who achieved objective responses (CR/PR)										
Biomarker- Bone Marrow Biopsy[r] &Aspirate **(Lymphoma)**	X	**If available**, bone marrow biopsy samples will be submitted to the Central Laboratory for biomarker analysis at any time performed (such as at the time of nodal CR by CT alone).															
Biomarker- Bone Marrow Biopsy &Aspirate **(CLL)**[r]	X	Bone marrow biopsy samples will be submitted to the Central Laboratory for biomarker analysis at any time performed.															

Table 8: Table of Events – Arm B - Durvalumab and Ibrutinib (Continued)

Events	Screening Period	Treatment Period													Follow-up	
		C1			C2		C3		C4		C5	C6-13	C14/ EOT-D	≥ C15	EOT	
	D -28 to -1	D1	D2&D 3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1		Safety D28 /D90	Efficacy[a]
Durvalumab IV Infusion		X			X		X		X		X	X					
Dispense Ibrutinib (PO)		X			X		X		X		X	X	X	X[s]			
Tumor Lysis Proph. (Allopurinol or equivalent) **recommended**		X	X	X													
Concomitant Medications/ Procedures	After signing informed consent through 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later.																
Adverse Events (AE)	After signing informed consent through 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later.																
Subsequent Antilymphoma/Anticancer Treatment Status	After signing informed consent until the subject dies, withdraws consent from the study, or for up to 24 months after his/her last durvalumab dose or disease progression, whichever date occurs later.																
Survival Status																	
Second Primary Malignancy (SPM) Assessment	After signing informed consent until the subject dies, withdraws consent from the study or for up to 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later.																

Abbreviations: ADA = anti-drug antibodies; BMB = bone marrow biopsy; C = cycle; CBC = complete blood count; CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; D = day; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EOT = end of treatment; EOT-D = end of durvalumab treatment; FC = flow cytometry; FCBP = female of childbearing potential; FDG = fluorodeoxyglucose; FDG-PET = fluorodeoxyglucose-positron emission tomography; FL = follicular lymphoma; fT3 = free triiodothronine; fT4 = free thyroxine; GGT = gamma glutamyl transferase; HBV = hepatitis B virus; IRT = integrated response technology; IV = intravenous; LDH = lactic dehydrogenase; MCL = mantle cell lymphoma; MRD = minimal residual disease; MZL = marginal zone lymphoma;

PBMC = peripheral blood mononuclear cells; PD = progressive disease; PK = pharmacokinetics; PO = orally; PR = partial response; PS = performance status; SLL = small lymphocytic lymphoma; SPM = second primary malignancy; WBC = white blood cell.

[a] Efficacy Follow up will be performed up to 24 months from subject's last durvalumab dose or disease progression, whichever occurs later. Following completion or discontinuation of durvalumab treatment per protocol for all subjects and completion of the primary analysis (data cutoff date 06 Mar 2019), subjects are no longer required to be followed for disease progression, subsequent antilymphoma/CLL therapy, and overall survival. Follow-up procedures, efficacy assessments, central labs, imaging, and survival data will no longer be collected in the CRFs.

[b] Subjects will have their blood pressure, and pulse, and body temperature measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (within an hour prior to start of durvalumab administration);
- At 30 minutes during the infusion (± 5 minutes);
- At the end of the infusion (at 60 minutes ± 5 minutes);
- In the 2-hour observation period post-infusion: every 30 minutes after the infusion (ie, 90, 120, 150, and 180 minutes from the start of the infusion) (± 5 minutes) – **for the first infusion only and then for subsequent infusions as clinically indicated**.
- If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated.

[c] Thyroid stimulating hormone (TSH), fT4, and fT3. Cycle 6 onward: TSH only, if TSH is abnormal, then reflex testing for fT4 and fT3.

[d] Direct antiglobulin test will be performed at site's local laboratory.

[e] Once a subject has experienced confirmed progression, or started a new antilymphoma/CLL therapy, no further scans, physicial examination, or laboratory assessments are required.

[f] Screening bone marrow biopsy is required in subjects with suspected bone marrow involvement by lymphoma per investigator's discretion.

[g] If an FDG-PET-CT is performed and confirms FDG-negative CR, BMB and aspirate are not required for subjects with aggressive histologies (eg, DLBCL and HL).

[h] Please see Section 6.4.1.4 for MRD assessments.

[i] In subjects with CLL, CT scan is highly recommended (unless its frequency exceeds local standards) to confirm suspected CR (by clinical and CBC-based) (within 8 weeks after clinical and CBC-based CR).

[j] In subjects with CLL, CT is required at Cycle 7 Day 1 (± 7 days) for only affected regions with abnormal findings at baseline.

[k] In subjects with CLL, BMB will be also performed to confirm suspected CR (by clinical, laboratory [including peripheral blood flow-negativity] and imaging) (within 12 weeks); and to evaluate cytopenia of uncertain cause (as clinically indicated).

[l] Please see Section 6.4.2.3 for further information about the MRD assessments in CLL.

[m] Please see Section 6.6.1 for PK sample collection time points for durvalumab.

[n] Please see Section 6.6.3 for PK sample collection time points for ibrutinib.

[o] Please see Section 6.7 for immunogenicity sample collection time points.

[p] In addition, it is strongly recommended to submit to the Central Laboratory any archival lymph node/tumor biopsy samples collected prior to study entry as well as any biopsy sample collected during the study for biomarker analysis.

[q] The only exception is that an archival diagnostic lymph node/tumor formalin fixed paraffin embedded (FFPE) biopsy acquired by a surgical or core needle biopsy within 3 months and with no intervening treatment prior to signing informed may be acceptable for enrollment in subjects with poorly accessible tumor following the discussion with the sponsor's medical monitor.

[r] In addition, it is strongly recommended to submit to the Central Laboratory any archival bone marrow biopsy samples collected prior to study entry as well as any biopsy samples collected during the study for biomarker analysis.

[s] For subjects remaining on ibrutinib treatment, study medication can be dispensed every 3 months with assessments done as per the investigator's discretion.

Detailed information (including visit windows) for each assessment is provided in Section 6.

Table 9: Table of Events – Arm C – Durvalumab and Rituximab ± Bendamustine

Events	Screening Period	Treatment Period									Follow-up	
		C1				C2-C6			C7-13	EOT-D/ EOT		
	D-28 to -1	D1	D2	D3	D 8, 15 & 22	D1	D2	D15	D1		Safety D28/D90	Efficacy[a]
Informed Consent	X											
IRT Registration	X	X	X			X	X		X	X		
Inclusion/Exclusion Criteria	X											
Demographics	X											
Medical History & Disease History	X											
Prior Anticancer Therapy	X											
Physical Examination & B symptoms	X	X				X			X	X	X	X (until PD)
Height	X											
Weight	X	X				X			X	X		
Body Surface Area	X	X										
Vital Sign Monitoring[b]	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X				X			X	X		
CIRS (only subjects > 80 years)	X											
12-lead ECG	X									X		
HBV Screening	X											
CBC & Differential	X	X		X	X	X		X	X	X	X	X (until PD)

Table 9: Table of Events – Arm C – Durvalumab and Rituximab ± Bendamustine (Continued)

Events	Screening Period	Treatment Period									Follow-up	
		C1				C2-C6			C7-13	EOT-D/ EOT		
	D-28 to -1	D1	D2	D3	D 8, 15 & 22	D1	D2	D15	D1		Safety D28/D90	Efficacy[a]
Clinical Chemistry (including LDH)	X	X		X	X	X		X	X	X	X	X (until PD)
GGT, Amylase, Lipase	X	X			X	X		X	X	X		
Thyroid Function Tests[c]	X	X			X (D15 only)	X (C2, C3, C4 & C6 only)		X (C2, C3, & C4 only)	X(C8, C10, & C12 only)	X	X (D90 only)	
Calculated Creatinine Clearance (serum)	X											
Coagulation	X	X			X (D15 only)	X			X	X	X (D90 only)	
Direct Antiglobulin- Blood[d] **(CLL only)**	X											
Quantitative Immunoglobulins	X									X		
Urinalysis	X									X		
Pregnancy Test for FCBP	X	X				X			X	X	X	
Efficacy Response Assessment						X (C4)			X (C7 & C10)	X	Every 6 cycles /months up to PD or start of a new antilymphoma/CLL therapy	
CT Scans (Neck, Chest, Abdomen &Pelvis) (contrast-enhanced unless contraindicated) **(Lymphoma)**	X					X (C4)			X (C7 & C10)	X	Every 6 cycles/months up to PD or start of a new antilymphoma/CLL therapy[e]	

Table 9: Table of Events – Arm C – Durvalumab and Rituximab ± Bendamustine (Continued)

Events	Screening Period	Treatment Period									Follow-up	
		C1				C2-C6			C7-13	EOT-D/ EOT		
	D-28 to -1	D1	D2	D3	D 8, 15 & 22	D1	D2	D15	D1		Safety D28/D90	Efficacy[a]
FDG-PET-CT **(FDG-avid Lymphoma)**	X (strongly recommended)	To confirm CR by CT scan alone at any time during the study (within 14 days following demonstration of nodal CR by CT scan alone)										
Bone Marrow Biopsy &Aspirate **(Lymphoma)**	X[f]	To confirm true CR (within 28 days of meeting the criteria for nodal CR by CT scan alone) except in subjects with no evidence of lymphomatous marrow involvement at baseline[g]										
MRD Assessment – Whole Blood **(in subjects with MCL and FL)**[h]		X	To confirm true CR (within 28 days of meeting the criteria for nodal CR by CT scan alone) except in subjects with no evidence of lymphomatous marrow involvement at baseline[g]									
MRD Assessment –Bone Marrow Aspirate **(in subjects with MCL and FL)**[h]		Within 28 days of meeting the criteria for PET negative CR and then every 3 cycles while on treatment or every 6 months in follow-up (as available) [h]										
CT Scans (Neck, Chest, Abdomen & Pelvis) (contrast-enhanced unless contraindicated)[i] **(CLL)**	X								X[j] (C7)			
Bone Marrow Biopsy & Aspirate[k] **(CLL)**	X								X (C7)	X		
MRD Assessment – Whole Blood **(in subjects with CLL)**[l]		X	Within 14 days of meeting the criteria for suspected CR (by clinical, CBC-based, and imaging assessments) and then every 3 cycles while on treatment or every 6 months in follow-up until evidence of clinical PD[l]									
MRD Assessment – Bone Marrow Aspirate **(in subjects with CLL)**[l]		Within 12 weeks of meeting the criteria for suspected CR by clinical, CBC-based, and imaging assessments and then every 3 cycles while on treatment or every 6 months in follow-up til evidence of clinical PD (as available)[l]										
PK- Blood Sampling for Durvalumab[m]		X	X	X	X	X (C2, C4 & C6)		X (C2)	X (C10)	X		

Table 9: Table of Events – Arm C – Durvalumab and Rituximab ± Bendamustine (Continued)

Events	Screening Period	Treatment Period									Follow-up	
		C1				C2-C6			C7-13	EOT-D/ EOT		
	D-28 to -1	D1	D2	D3	D 8, 15 & 22	D1	D2	D15	D1		Safety D28/D90	Efficacy[a]
Immunogenicity (ADA)-Blood Sample[n]		X				X (C2, C4, & C6)			X (C10)	X		
Biomarker-Saliva (pharmacogenomics)	X											
Biomarker- PBMC Isolation	X							X (C2 & C4)		X		
Biomarker-Whole Blood for Immunophenotyping	X	X			X (D8 & D15 only)	X (C2)		X (C2)				
Biomarker-Serum	X	X				X (C2)						
Biomarker-Plasma (Cytokines / Soluble factors)	X	X				X (C2)		X (C2, C3 & C4)		X		
Biomarker- Tumor Biopsy[o] **(Lymphoma)**	X[p]					-Any time during C2 (recommended) and - At the time of disease progression (within 14 days) in subjects who achieved objective responses (CR/PR)						
Biomarker- Bone Marrow Biopsy &Aspirate[q] **(Lymphoma)**	X	**If available**, bone marrow biopsy samples will be submitted to the Central Laboratory for biomarker analysis at any time performed (such as at the time of nodal CR by CT alone).										
Biomarker- Bone Marrow Biopsy & Aspirate[q] **(CLL)**	X	Bone marrow biopsy samples will be submitted to the Central Laboratory for biomarker analysis at any time performed.										
Durvalumab IV Infusion		X				X			X			
Bendamustine IV Infusion		X	X			X	X					

Table 9: Table of Events – Arm C – Durvalumab and Rituximab ± Bendamustine (Continued)

Events	Screening Period	Treatment Period									Follow-up	
		C1				C2-C6			C7-13	EOT-D/ EOT		
	D-28 to -1	D1	D2	D3	D 8, 15 & 22	D1	D2	D15	D1		Safety D28/D90	Efficacy[a]
Rituximab IV Infusion			X				X					
Drug accountability		X	X			X	X		X			
Tumor Lysis Prophylaxis-recommended		X	X	X	X							
Concomitant Medications/ Procedures	After signing informed consent through 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later.											
Adverse Events (AE)	After signing informed consent through 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later.											
Subsequent Antilymphoma/Anticancer Treatment Status	After signing informed consent until the subject dies, withdraws consent from the study or for up to 24 months from the date of each subject's last durvalumab dose.											
Survival Status												
Second Primary Malignancy Assessment (SPM)	After signing informed consent until the subject dies, withdraws consent from the study or for up to 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later.											

Abbreviations: ADA = anti-drug antibodies; BMB = bone marrow biopsy; C = cycle; CBC = complete blood count; CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; D = day; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram ; ECOG= Eastern Cooperative Oncology Group; EOT = end of treatment; EOT-D = end of durvalumab treatment; FC = flow cytometry; FCBP = female of childbearing potential; FDG = fluorodeoxyglucose; FDG-PET = fluorodeoxyglucose-positron emission tomography; FL = follicular lymphoma; fT3 = free triiodothronine; fT4 = free thyroxine; GGT = gamma glutamyl transferase; HBV = hepatitis B virus; IRT = Integrated response technology; IV = intravenous; HL = Hodgkin lymphoma; LDH = lactic dehydrogenase; MCL = mantle cell lymphoma; MRD = minimal residual disease; MZL = marginal zone lymphoma; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PK = pharmacokinetics; PR = Partial Response; PS = performance status; SPM = second primary malignancy; WBC = white blood cell.

[a] Efficacy Follow-up will be performed up to 24 months from subject's last durvalumab dose. Following completion or discontinuation of durvalumab treatment per protocol for all subjects and completion of the primary analysis (data cutoff date 06 Mar 2019), subjects are no longer required to be followed for disease progression, subsequent antilymphoma/CLL therapy, and overall survival. Follow-up procedures, efficacy assessments, central labs, imaging, and survival data will no longer be collected in the CRFs.

[b] Subjects will have their blood pressure, and pulse, and measured before, during and after the infusion at the following times (based on a 60-minute infusion):
- At the beginning of the infusion (within an hour prior to start of durvalumab administration);
- At 30 minutes during the infusion (± 5 minutes);
- At the end of the infusion (at 60 minutes ± 5 minutes);
- In the 2-hour observation period post-infusion: every 30 minutes after the infusion (ie, 90, 120, 150, and 180 minutes from the start of the infusion) (± 5 minutes) – **for the first infusion only and then for subsequent infusions as clinically indicated**.
- If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated.

[c] Thyroid stimulating hormone (TSH), fT4, and fT3. Cycle 6 onward: TSH only, if TSH is abnormal, then reflex testing for fT4 and fT3.
[d] Direct antiglobulin test will be performed at site's local laboratory.
[e] Once a subject has experienced confirmed progression, or started a new antilymphoma/CLL therapy, no further scans, physicial examination, or laboratory assessments are required.
[f] Screening bone marrow biopsy is required in subjects with suspected bone marrow involvement by lymphoma per investigator's discretion.
[g] If an FDG-PET-CT is performed and confirms FDG-negative CR, BMB and aspirate is not required for subjects with aggressive histologies (eg, DLBCL and HL).
[h] Please see Section 6.4.1.4 for MRD assessment
[i] In subjects with CLL, CT scan is highly recommended (unless its frequency exceeds local standards) to confirm suspected CR (by clinical and CBC-based) (within 8 weeks after clinical and CBC-based CR).
[j] In subjects with CLL, CT is required at Cycle 7 Day 1 (± 7 days) for only affected regions with abnormal findings at baseline.
[k] In subjects with CLL, BMB will be also performed to confirm suspected CR (by clinical, laboratory [including peripheral blood flow-negativity] and imaging) (within 12 weeks); and to evaluate cytopenia of uncertain cause (as clinically indicated).
[l] Please see Section 6.4.2.3 for MRD assessment in CLL.
[m] Please see Section 6.6.1 for PK sample collection time points for durvalumab.
[n] Please see Section 6.7 for immunogenicity sample collection time points.
[o] In addition, it is strongly recommended to submit to the Central Laboratory any archival lymph node/tumor biopsy samples collected prior to study entry as well as any biopsy sample collected during the study for biomarker analysis.
[p] The only exception is that an archival diagnostic lymph node/tumor formalin fixed paraffin embedded (FFPE) biopsy acquired by a surgical or core needle biopsy within 3 months and with no intervening treatment prior to signing informed consent may be acceptable for enrollment in subjects with poorly accessible tumor following the discussion with the sponsor's medical monitor.
[q] In addition, it is strongly recommended to submit to the Central Laboratory any archival bone marrow biopsy samples collected prior to study entry as well as any biopsy samples collected during the study for biomarker analysis.

Detailed information (including visit windows) for each assessment is provided in Section 6.

Table 10: Table of Events – Arm D – Durvalumab Monotherapy

Events	Screening Period	Treatment Period												Follow-up	
		C1			C2		C3		C4		C5	C6-13 (/C6-C19[a])	EOT-D/ EOT		
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1		Safety D28/ D90	Efficacy[b]
Informed Consent	X														
IRT Registration	X	X			X		X		X		X	X	X		
Inclusion/Exclusion Criteria	X														
Demographics	X														
Medical History & Disease History	X														
Prior Anticancer Therapy	X														
Physical Examination & B symptoms	X	X			X		X		X		X	X	X	X	X (until PD)
Height	X														
Weight	X	X			X		X		X		X	X	X		
Vital Sign Monitoring[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X			X		X		X		X	X	X		
CIRS (only subjects > 80 years)	X														
12-lead ECG	X												X		
HBV Screening	X														
CBC & Differential	X	X	X (D3 only)	X	X	X	X	X	X	X	X	X	X	X	X (until PD)

Table 10: Table of Events – Arm D – Durvalumab Monotherapy (Continued)

Events	Screening Period	Treatment Period												Follow-up	
		C1			C2		C3		C4		C5	C6-13 (/C6-C19[a])	EOT-D/ EOT		
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1		Safety D28/ D90	Efficacy[b]
Clinical Chemistry (including LDH)	X	X	X (D3 only)	X	X	X	X	X	X	X	X	X	X	X	X (until PD)
GGT, Amylase, Lipase	X	X		X	X	X	X	X	X	X	X	X	X		
Thyroid Function Tests[d]	X	X		X (D15 only)	X	X	X	X	X	X		X (C6, C8, C10, C12/ if applicable: C14, C16, C18 only)	X	X (D90 only)	
Calculated Creatinine Clearance (serum)	X														
Coagulation	X	X		X (D15 only)	X		X		X		X	X	X	X (D90 only)	
Direct Antiglobulin-Blood **(CLL only)**[e]	X														
Quantitative Immunoglobulins	X												X		
Urinalysis	X												X		
Pregnancy Test for FCBP	X	X			X		X		X		X	X	X	X	
Efficacy Response Assessment									X			X (C7 & C10)	Every 6 cycles/months up to PD or start of a new antilymphoma/CLL therapy		

Table 10: Table of Events – Arm D – Durvalumab Monotherapy (Continued)

Events	Screening Period	Treatment Period												Follow-up	
		C1			C2		C3		C4		C5	C6-13 (/C6-C19 [a])	EOT-D/ EOT		
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1		Safety D28/ D90	Efficacy[b]
CT Scans (Neck, Chest, Abdomen &Pelvis) (contrast-enhanced unless contraindicated) **(Lymphoma)**	X								X			X (C7 & 10)	X	Every 6 cycles/months up to PD or start of a new antilymphoma/CLL therapy	
FDG-PET-CT **(FDG-avid Lymphoma)**	X (strongly recommended)								To confirm CR by CT scan alone at any time during the study (within 14 days following demonstration of nodal CR by CT scan alone)						
Bone Marrow Biopsy &Aspirate **(Lymphoma)**	X[g]								To confirm true CR (within 28 days of meeting the criteria for nodal CR by CT scan alone) except in subjects with no evidence of lymphomatous marrow involvement at baseline[h]						
MRD Assessment – Whole Blood **(in subjects with MCL and FL)**		X							Within 28 days of meeting the criteria for PET negative CR and then every 3 cycles while on treatment or every 6 months in follow-up until evidence of clinical PD[i]						
MRD Assessment – Bone Marrow Aspirate **(in subjects with MCL and FL)**[i]									Within 28 days of meeting the criteria for PET negative CR and then every 3 cycles while on treatment or every 6 months in follow-up (as available) [i]						
CT Scans (Neck, Chest, Abdomen & Pelvis) (contrast-enhanced unless contraindicated) **(CLL)**[j]	X											X[k] (C7)			
Bone Marrow Biopsy & Aspirate **(CLL)**	X											X (C7)	X		

Table 10: Table of Events – Arm D – Durvalumab Monotherapy (Continued)

Events	Screening Period	Treatment Period												Follow-up	
		C1			C2		C3		C4		C5	C6-13 (/C6-C19[a])	EOT-D/ EOT		
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D 1	D15	D1	D15	D1	D1		Safety D28/ D90	Efficacy[b]
MRD Assessment – Whole Blood **(in subjects with CLL)**[m]		X							Within 14 days of meeting the criteria for suspected CR (by clinical, CBC-based, and imaging assessments) and then every 3 cycles while on treatment or every 6 months in follow-up until evidence of clinical PD[m]						
MRD Assessment – Bone Marrow Aspirate **(in subjects with CLL)**[m]									Within 12 weeks of meeting the criteria for suspected CR by clinical, CBC-based, and imaging assessments and then every 3 cycles while on treatment or every 6 months in follow-up til evidence of clinical PD (as available)[m]						
PK- Blood Sampling[n] for Durvalumab		X	X	X	X	X			X			X (C6 & C10)	X		
Immunogenicity (ADA)- Blood Sample[o]		X			X				X			X (C6 & C10)	X		
Biomarker- Saliva (pharmacogenomics)	X														
Biomarker- PBMC Isolation	X					X				X			X		
Biomarker-Whole Blood for Immunophenotyping	X	X		X (D8 & D15 only)	X	X									
Biomarker-Serum	X	X			X										
Biomarker-Plasma (Cytokines / Soluble factors)	X	X			X	X		X		X			X		

Table 10: Table of Events – Arm D – Durvalumab Monotherapy (Continued)

Events	Screening Period	Treatment Period												Follow-up	
		C1			C2		C3		C4		C5	C6-13 (/C6-C19[a])	EOT-D/ EOT		
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1		Safety D28/ D90	Efficacy[b]
Biomarker-Tumor Biopsy**(Lymphoma)**[p]	X[q]				X (recommended)		At the time of disease progression (within 14 days) in subjects who achieved objective responses (CR/PR)								
Biomarker- Bone Marrow Biopsy &Aspirate **(Lymphoma)**[r]	X	**If available**, bone marrow biopsy samples will be submitted to the Central Laboratory for biomarker analysis at any time performed (such as at the time of nodal CR by CT alone).													
Biomarker- Bone Marrow Biopsy & Aspirate **(CLL)**[r]	X	Bone marrow biopsy samples will be submitted to the Central Laboratory for biomarker analysis at any time performed.													
Durvalumab IV Infusion		X			X		X		X		X	X			
Drug Accountability		X			X		X		X		X	X	X		
Local IFRT **(optional)**					At the time of PD, subjects may receive local IFRT to a single involved nodal site based on the investigator's discretion[s]										
Tumor Lysis Prophylaxis (Allopurinol or equivalent) **recommended**		X	X	X											
Concomitant Medications/ Procedures	After signing informed consent through 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later.														
Adverse Events (AE)	After signing informed consent through 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later.														

Table 10: Table of Events – Arm D – Durvalumab Monotherapy (Continued)

Events	Screening Period	Treatment Period											Follow-up	
		C1			C2		C3		C4		C5	C6-13 (/C6-C19[a])	EOT-D/ EOT	
	D -28 to -1	D1	D2&D3	D8, D15 & D22	D1	D15	D1	D15	D1	D15	D1	D1		Safety D28/ D90	Efficacy[b]
Subsequent Antilymphoma/Anti-cancer Treatment Status	After signing informed consent until the subject dies, withdraws consent from the study or for up to 24 months from the date of each subject's last dose.														
Survival Status															
Second Primary Malignancy Assessment (SPM)	After signing informed consent until the subject dies, withdraws consent from the study or for up to 90 days after the last dose of durvalumab.														

Abbreviations: ADA = anti-drug antibodies; BMB = bone marrow biopsy; C = cycle; CBC = complete blood count; CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; D = day; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram ; ECOG= Eastern Cooperative Oncology Group; EOT = end of treatment; EOT-D = end of durvalumab treatment; FCBP = female of childbearing potential; FDG = fluorodeoxyglucose; FDG-PET = fluorodeoxyglucose-positron emission tomography; FL = follicular lymphoma; GGT = gamma glutamyl transferase; HBV = hepatitis B virus; IFRT = involved field radiation therapy; IRT = Integrated response technology; LDH = lactic dehydrogenase; MCL = mantle cell lymphoma; MRD = minimal residual disease; IV = intravenous; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PK = pharmacokinetics; PR = partial response; PS= performance status; SPM = second primary malignancy; WBC = white blood cell.

[a] Subjects who receive local IFRT, 2 Gy on each of 2 consecutive days to one tumor site, as an additional therapy to durvalumab will continue to follow the Arm D schedule. Following IFRT, subjects will receive durvalumab for up to **6 cycles** based on the investigator's medical judgment. Please see Sections 3.1.2 and 6.2 for further information.

[b] Efficacy Follow-up will be performed up to 24 months from subject's last durvalumab dose. Following completion or discontinuation of durvalumab treatment per protocol for all subjects and completion of the primary analysis (data cutoff date 06 Mar 2019), subjects are no longer required to be followed for disease progression, subsequent antilymphoma/CLL therapy, and overall survival. Follow-up procedures, efficacy assessments, central labs, imaging, and survival data will no longer be collected in the CRFs.

[c] Subjects will have their blood pressure, pulse and body temperature measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (within an hour prior to start of durvalumab administration);
- At 30 minutes during the infusion (± 5 minutes);
- At the end of the infusion (at 60 minutes ± 5 minutes);
- In the 2- hour observation period post-infusion: every 30 minutes after the infusion (ie, 90, 120, 150, and 180 minutes from the start of the infusion) (± 5 minutes) – **for the first infusion only and then for subsequent infusions as clinically indicated**.

- If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated.

[d] Thyroid stimulating hormone (TSH), fT4, and fT3. Cycle 6 onward: TSH only, if TSH is abnormal, then reflex testing for fT4 and fT3.
[e] Direct antiglobulin test will be performed at site's local laboratory.
[f] Once a subject has experienced confirmed progression, or started a new antilymphoma/CLL therapy, no further scans, physical examination, or laboratory assessments are required.
[g] Screening bone marrow biopsy is required in subjects with suspected bone marrow involvement by lymphoma per investigator's discretion.
[h] If an FDG-PET-CT is performed and confirms FDG-negative CR, BMB and aspirate is not required for subjects with aggressive histologies (eg, DLBCL and HL).
[i] Please see Section 6.4.1.4 for MRD assessments.
[j] In subjects with CLL, CT scan is highly recommended (unless its frequency exceeds local standards) to confirm suspected CR (by clinical and CBC-based) (within 8 weeks after clinical and CBC-based CR).
[k] In subjects with CLL, CT is required at Cycle 7 Day 1 (± 7 days) for only affected regions with abnormal findings at baseline.
[l] In subjects with CLL, BMB will be also performed to confirm suspected CR (by clinical, laboratory [including peripheral blood flow-negativity] and imaging) (within 12 weeks); and to evaluate cytopenia of uncertain cause (as clinically indicated).
[m] Please see Section 6.4.2.3 for MRD assessments in CLL.
[n] Please see Section 6.6.1 for PK sample collection time points for durvalumab.
[o] Please see Section 6.7 for immunogenicity sample collection time points.
[p] In addition, it is strongly recommended to submit to the Central Laboratory any archival lymph node/tumor biopsy samples collected prior to study entry as well as any biopsy sample collected during the study for biomarker analysis.
[q] The only exception is that an archival diagnostic lymph node/tumor formalin fixed paraffin embedded (FFPE) biopsy acquired by a surgical or core needle biopsy within 3 months and with no intervening treatment prior to signing informed consent may be acceptable for enrollment in subjects with poorly accessible tumor following the discussion with the sponsor's medical monitor.
[r] In addition, it is strongly recommended to submit to the Central Laboratory any archival bone marrow biopsy samples collected prior to study entry as well as any biopsy samples collected during the study for biomarker analysis.
[s] Please see Sections Section 3.1.2, Section 6.2, and Section 7.1.6 for further information.

Detailed information (including visit windows) for each assessment is provided in Section 6.

6. PROCEDURES

Any questions regarding the protocol should be directed to the sponsor's medical monitor or designee.

Arm A is discontinued to the enrollment of new subjects. 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.

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility after signing the informed consent form. These evaluations must be completed within 28 days of administration of the first dose (Cycle 1 Day 1 [C1D1]) unless noted otherwise below.

Inclusion/exclusion criteria must be reviewed and cleared prior to treatment assignment. Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

- **Informed Consent** must be obtained prior to beginning any assessments solely for the purpose of this study. Standard of care assessments performed prior to signing the ICF (as described in the protocol) may be used for this study, assuming they meet the protocol requirements and following discussion with the sponsor's medical monitor or designee. The subject may withdraw consent at any time for all or certain aspects of the study as follows:
  - Withdraw consent for study treatment, but allow Follow-up Period assessments and data collection on subsequent antilymphoma/CLL therapy and PFS.
  - Withdraw consent for study treatment and Follow-up Period assessments, but allow data collection on subsequent antilymphoma/CLL therapy and OS.
  - Withdraw all consent.

If screening assessments are performed within 48 hours of Cycle 1 Day 1, safety laboratory and physical examinations including electrocardiogram (ECG), need not be repeated at Cycle 1 Day 1. The following will be performed or assessed at Screening (in all treatment arms) as specified in the Tables of Events Section 5, after informed consent has been obtained:

- **Interactive response technology (IRT)** registration.
- **Demographics** will include date of birth, sex, race, and ethnicity-if allowed by local regulations.
- **Complete medical history** will be documented by a qualified clinician at the time of the Screening Visit. The medical history will be general enough to document common comorbid conditions as well as specific enough to confirm any condition against the eligibility criteria, and will document whether the identified conditions are active or inactive at the time of enrollment. Relevant medical history findings will be recorded within the source document and the CRF. Medical and medication history will be assessed in relation to the eligibility criteria as listed in Section 4.

- **Disease history** will include specific information regarding diagnosis, characteristics, and histology including grade.
- **Prior anticancer therapies** will include surgery, radiation, systemic, or stem cell transplant (only autologous stem cell transplant is allowed) for lymphoma or CLL.
- **Prior and concomitant medication evaluation** will include those taken ≤ 28 days before screening, except for those taken for lymphoma or CLL.
- **Prior and concomitant procedures** will include all procedures occurring ≤ 28 days before screening.
- **Physical examination** including evaluation of lymph nodes, spleen and liver will be performed.
- **B symptoms** including fever greater than 38°C, drenching night sweats, and unintentional weight loss of > 10% of normal body weight over a period of 6 months or less.
- **Body weight and height** (height at the Screening Visit only) will be measured.
- **Body surface area (BSA)** will be calculated using the subject's height and weight according to local pharmacy practice if the subject will receive rituximab or bendamustine.

It is up to pharmacist and investigator discretion whether BSA will be recalculated prior to preparing every cycle of rituximab or bendamustine, or whether the BSA calculated prior to the first dose (Cycle 1 Day 1) will be used throughout the study. If BSA is to be recalculated, the same calculation method should be used throughout the study per subject.

- **Vital signs** will include blood pressure, pulse, and body temperature.
- **ECOG Performance Status** (Oken, 1982) will be scored according to Table 11.

Table 11: Performance Status by Eastern Cooperative Oncology Group Scale

Score	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

- **Modified Cumulative Illness Rating Scale (CIRS)** is to be scored at the Screening Visit only for subjects who are > 80 years of age. Each organ system is scored separately according to Appendix I and includes all of the following organ specific categories: cardiac, hypertension, vascular, respiratory, eye/ear/nose/throat/larynx, upper gastrointestinal, lower gastrointestinal, hepatic/biliary, renal, genitourinary, musculoskeletal, endocrine/metabolic, neurological, and psychiatric (Salvi, 2008a; Salvi, 2008b). Lymphoma or CLL disease or related organ damage should not be assessed in this rating scale. If there are 2 or more illnesses/impairments in one organ system, the illness/impairment with the highest severity will be evaluated. Additional information for evaluating each organ system is provided in Appendix I.
- **12-lead electrocardiogram (ECG)** will be recorded.

Screening safety laboratory tests (except for direct antiglobulin test in subjects with CLL) will be performed at the designated central laboratory; however, in urgent cases, local laboratory results may be used to guide clinical decisions and dose modifications, and, that data must be submitted to Celgene in the CRF, and whenever possible, a concurrent sample should be sent to the Central Laboratory. Refer to the Laboratory Manual for sample handling, storage, and shipment instructions.

Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, as necessary:

- **Hepatitis B virus (HBV) testing** will include hepatitis B surface antigen (HBsAg), antibody to the hepatitis B surface antigen (anti-HBs), and antibody to the hepatitis B core antigen (anti-HBc). If a subject is anti-HBc positive, the Central Laboratory will automatically perform a quantitative polymerase chain reaction test to measure viral DNA load.
- **Complete blood count (CBC) with absolute differential** will include hematocrit, hemoglobin, white blood cell count (WBC) with differential, and platelet count.
- **Clinical chemistry and other laboratory tests** will include albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate transaminase (AST/SGOT), bilirubin (total, direct, and indirect), calcium, chloride, creatinine, glucose, phosphorous, potassium, sodium, total protein, serum urea/blood urea nitrogen (BUN), and uric acid.
- **Lactic dehydrogenase** will be tested.
- **Gamma glutamyl transferase, amylase, and lipase** will be tested.
- **Thyroid function tests** will include thyroid stimulating hormone (TSH), free thyroxine (fT4), and free triiodothronine (fT3).
- **Calculated creatinine clearance (CrCl)** will be estimated using the Cockcroft-Gault formula by the Central Laboratory**:**

  CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]; for females, the formula is multiplied by 0.85 (Cockcroft, 1976).

- **Coagulation tests** will include prothrombin time, international normalized ratio (INR) and partial thromboplastin time (PTT or activated PTT).
- **Direct antiglobulin test** (also known as direct Coombs test) will be performed for subjects with CLL (Arms B, C, and D) at site's local laboratory.
- **Quantitative immunoglobulins** including IgG, IgA, and IgM will be measured.
- **Biomarker saliva and blood sample(s)** will be collected as outlined in Section 6.8.
- **Urinalysis** (a urine dipstick may be used) will include color, appearance, specific gravity, pH, glucose, ketones, blood, bilirubin, and protein. A microscopic examination will be performed if urinalysis result is abnormal.
- **Pregnancy testing** (Arms B, C, and D) is required for all females of childbearing potential (FCBP). A urine (or serum) pregnancy tests (with a sensitivity of at least 25 mIU/mL will be performed to assess subject eligibility at Screening and within 48 hours prior to the first administration of IP in Arms B, C, and D. Negative results (2 negative results: one performed during the Screening Visit and one performed within 48 hours of Cycle 1 Day 1 prior to dosing) are required for IP administration.

  Pregnancy testing for subjects receiving lenalidomide (applies to subjects **in Arm A** and subjects in **Arm D** who will receive **subsequent lenalidomide treatment** at the time of progression): FCBP must have 2 negative urine (or serum) pregnancy tests (with a sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days and the second pregnancy test must be performed within 24 hours prior to first lenalidomide dose. Negative results are required for IP administration.
- **Counseling about pregnancy precautions and the potential risks of fetal exposure** (applies to all subjects in Arm A and subjects in Arm D who will receive additional lenalidomide treatment at the time of progression): must be conducted at Screening and before receiving any IP.

Please consult the Lenalidomide Pregnancy Prevention Risk Management Plan (Appendix F) for details.

- **Biomarker biopsy sample (lymph node or tumor) collection** is mandatory from all subjects with lymphoma during Screening and must be also submitted to the Central Laboratory for biomarker analysis defined in Section 6.8.

The only exception is that an archival lymph node/tumor formalin-fixed paraffin-embedded (FFPE) biopsy acquired by a surgical or core needle biopsy within 3 months and with no intervening treatment prior to signing informed consent may be acceptable for enrollment in subjects with poorly accessible tumor following the discussion with the sponsor's medical monitor.

Subject eligibility will be based on the investigators' and local pathologists' assessment of the histopathology diagnosis.

- **Bone marrow biopsy and aspirate** collection during Screening is mandatory from subjects with CLL and per investigator's discretion in subjects with suspected bone

marrow involvement by lymphoma. The samples must be submitted to the Central Laboratory for biomarker analysis defined in Section 6.8.

- **Computed tomography (CT) scans (neck, chest, and abdomen and pelvis) or integrated** fluorodeoxyglucose-positron emission tomography with CT **(FDG-PET-CT) (whole body)** should be performed during Screening. Please see Section 6.4 for further details.
- **Adverse event/adverse events of special interest assessment** (including SPMs) begin when the subject signs the informed consent form.
- **Survival status** will be assessed.
- **Subsequent antilymphoma/anticancer treatments status** information will be collected.

6.2. Treatment Period

Subjects will begin treatment following confirmation of eligibility. For all subsequent visits, an administrative window of ± 3 days for study Day 1 visits and ± 1 (except for otherwise noted) for scheduled interim study visits (eg, Day 18, 15, 22 visits) are allowed.

For subjects on ibrutinib, for all subsequent visits, clinic visits will be in accordance with standard of care per the investigator's discretion. No data will be collected and eCRFs will not be completed. The investigator remains responsible to monitor safety, record adverse events (AEs)/serious adverse events (SAEs)/second primary malignancies(SPMs) in source documents, and report SAEs and SPMs to Celgene Drug Safety.

Prior to the administration of first dose on Cycle 1 Day 1, the laboratory results must be reviewed by the investigator to reconfirm subject eligibility. If the central safety laboratory results are not available for review yet, then the local safety laboratory results can be used to reconfirm subject eligibility. Blood samples for safety laboratories must be always collected and submitted to the Central Laboratory according to the schedule in Sections 5 and below.

Subjects who receive lenalidomide should have at least a 7-day rest between two 21-day treatment periods and therefore this should be taken into consideration when applying the visit window of ± 3 days.

If assessments are performed within 48 hours of Day 1 of each cycle, safety laboratory and physical examinations need not be repeated on Day 1.

Treatment cycles are 28 days in duration and will occur as described in Section 7.2.

Evaluations will be performed at the frequency specified in Section 5. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified (such as PK or Pd).

Unscheduled assessments may be performed as clinically indicated (eg, more frequent monitoring of relevant blood tests, in case of adverse event, ECG, HBV testing, urinalysis, scans), and those visits should be also recorded in the subject's source documents and CRF.

The following evaluations will be performed as specified in the Table of Events:

- **Adverse event assessment/adverse events of special interest** (including SPM).

- **Tumor lysis prophylaxis (TLS)** is recommended. Subjects will receive TLS prophylaxis or treatment (allopurinol or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of treatment administration in the first cycle, or as clinically indicated. Hydration levels should be adjusted according to age and clinical status. To monitor for TLS, the subjects will have close monitoring of blood chemistry during the first few cycles and additionally as clinically indicated. Please see Section 8.1.7 for further details.
- **Concomitant medications/procedures evaluation.**
- **Physical examination** including evaluation of lymph nodes, spleen and liver will be performed. Documentation of any enlargement of the lymph nodes, spleen and/or liver should be recorded in the source document and CRF.
- **B symptoms** including fever greater than 38°C, drenching night sweats, and unintentional weight loss of > 10% of normal body weight over a period of 6 months or less.
- **Body weight** will be measured.
- **Body surface area** (as required per the site's local practice for rituximab or bendamustine).
- **Vital signs** will include blood pressure, pulse, and body temperature.

Subjects will have their blood pressure, pulse and body temperature measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (within an hour prior to start of durvalumab administration)
- At 30 minutes during the infusion (± 5 minutes)
- At the end of the infusion (at 60 minutes ± 5 minutes)
- In the 2-hour observation period post-infusion: every 30 minutes after the infusion (ie, 90, 120, 150, and 180 minutes from the start of the infusion) (± 5 minutes) – **for the first infusion only and then for subsequent infusions as clinically indicated**

  If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated.

- **ECOG Performance Status** will be scored according to Table 11.

Safety laboratory tests will be performed at the designated central laboratory; however, in urgent cases, local laboratory results may be used to guide clinical decisions and dose modifications, and that data must be submitted to Celgene in the CRF, and whenever possible, a concurrent sample should be sent to the Central Laboratory.

Refer to the Laboratory Manual for sample handling, storage, and shipment instructions.

- **Complete blood count with absolute differential** will include hematocrit, hemoglobin, WBC with differential, and platelet count.
- **Clinical chemistry and other laboratory tests** will include albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, bilirubin (total, direct, and indirect), calcium, chloride, creatinine, glucose, phosphorous, potassium, sodium, total protein, serum urea/ BUN and uric acid.
- **Lactic dehydrogenase** will be tested.
- **Gamma glutamyl transferase, amylase, and lipase** will be tested.
- **Thyroid function tests** will include:
  - Cycles 1 – 4: thyroid stimulating hormone (TSH), free thyroxine (fT4), and free triiodothronine (fT3) and
  - Cycle 6 onward: TSH, if TSH is abnormal, then reflex testing for fT4 and fT3.
- **Coagulation tests** will include prothrombin time, international normalized ratio (INR) and partial thromboplastin time (PTT or activated PTT).
- **12-lead ECG** will be performed on Cycle 14 Day 1 (as applicable) or at the End of Treatment for durvalumab (EOT-D).
- **Urinalysis** (a urine dipstick may be used) will include color, appearance, specific gravity, pH, glucose, ketones, blood, bilirubin, and protein. A microscopic examination will be performed if urinalysis result is abnormal. This will be performed on Cycle 14 Day 1 (as applicable) or at the End of Treatment for durvalumab (EOT-D).
- **Quantitative immunoglobulins** including IgG, IgA, and IgM will be measured on Cycle 14 Day 1 (as applicable) or at the End of Treatment for durvalumab (EOT-D).
- **Pharmacokinetic, immunogenicity, and biomarker blood sample(s) and tumor samples** will be collected as outlined in Sections 6.6, 6.7, and 6.8.
- **Biomarker biopsy sample (lymph node or tumor) collection** is strongly recommended from all subjects with lymphoma anytime during Cycle 2 for biomarker analysis defined in Section 6.8.
- **Pregnancy test** is required for all FCBP subjects. A urine (or serum) pregnancy test (with a sensitivity of at least 25 mIU/mL) will be performed within 48 hours prior to Day 1 dosing in each cycle (**except lenalidomide**). Negative results are required for IP administration.

  Pregnancy testing for lenalidomide (applies to all subjects **in Arm A** and subjects in **Arm D** who will receive **subsequent lenalidomide treatment** at the time of progression): FCBP must have negative urine (or serum) pregnancy test (with a sensitivity of at least 25 mIU/mL) within 24 hours prior to lenalidomide dosing on Day 1 of each cycle. Pregnancy testing will be done weekly in the first cycle. For FCBP with irregular menstrual cycles, pregnancy testing will also be performed on Day 15 of each cycle. Negative results are required for IP administration.

- **Lenalidomide Counseling** (applies to subjects in Arm A or subjects in Arm D who will receive additional lenalidomide treatment at the time of progression): must be conducted while on treatment, at a minimum of every 28 days for all subjects. Please consult the Lenalidomide Pregnancy Prevention Risk Management Plan (Appendix F) for details.
- **Efficacy assessments for lymphoma and CLL** (including contrast-enhanced CT scans, FDG-PET-CT, bone marrow biopsy and aspirate, and minimal residual disease [MRD] assessments for CLL, MCL, and FL) are described in detail in Section 6.4.
- **Interactive response technology** registration.
- **Addition of combination agent or local IFRT to durvalumab monotherapy at the time of progression:**

For subjects in the monotherapy arm, Arm D, at the time of disease progression, the investigator may add study treatments previously investigated once a dose level of a relevant combination therapy is deemed as tolerable by the dedicated SRC (ie, rituximab ± either lenalidomide* or bendamustine; or monotherapy ibrutinib), or local IFRT with durvalumab, if subjects meet the criteria defined in Section 3.1.2.

The add-on combination treatment with lenalidomide ± rituximab is no longer allowed.*

Subjects who receive a combination agent other than local IFRT will follow the visit schedules and assessments specific to each combination agent (eg, the Arm A visit schedule and assessments starting from Cycle 1 Day 1 will be followed by subjects who receive lenalidomide and rituximab in addition to durvalumab*). Those subjects will be treated according to the treatment schedules described for each arm in Section 7.2 based on the investigator's medical judgment. Pharmacokinetic samples for durvalumab will be collected following the addition of a combination agent. No PK samples for lenalidomide or ibrutinib will be collected.

Subjects who receive local IFRT, 2 Gy on each of 2 consecutive days to one tumor site, as additional therapy will continue to follow the Arm D schedule. Following IFRT, subjects will receive durvalumab for up to an additional 6 cycles (eg, if a subject receives local IFRT following disease progression documented at the end of Cycle 13, he/she may receive 6 additional durvalumab doses, up to Cycle 19), or will complete the remaining scheduled durvalumab doses (ie, 13 cycles) based on the investigator's medical judgment.

The sponsor's medical monitor should be contacted prior to adding a combination agent to durvalumab.

- **Survival status** will be assessed.
- **Subsequent antilymphoma/anticancer treatments status** information will be collected.

6.2.1. End of Treatment

An end of all treatment (EOT) evaluation will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

In Arm A (indolent lymphoma), Arm C, and Arm D, the EOT for all study treatments and the EOT-D will be the same visit unless subjects discontinue durvalumab treatment (earlier than Cycle 13) due to toxicity. Please see Table 7, Table 8, Table 9, and Table 10.

In Arm A (aggressive lymphoma) and Arm B, EOT visit for all study treatments will occur after EOT-D which is expected to be the same visit with Cycle 14 Day 1 as the combination treatment (ie, lenalidomide or ibrutinib) may continue beyond Cycle 13 (last scheduled durvalumab dose) until disease progression, unacceptable toxicity, starts new therapy, or discontinuation for any other reason, ie, subject withdraws consent or discontinues per investigator's discretion. A few assessments such as 12-lead ECG, quantitative immunoglobulins, urinalysis, the laboratory tests including gamma glutamyl transferase, amylase, lipase, TSH, fT4, and fT3, coagulation, and immunogenicity assessment will be performed at the EOT-D visit. Please see Table 7 and Table 8.

The following evaluations will be performed as specified in the Table of Events in Section 5:

- **Adverse event assessment/adverse events of special interest** (including SPM).
- **Concomitant medications/procedures evaluation.**
- **Physical examination** including evaluation of lymph nodes, spleen and liver will be performed. Documentation of any enlargement of the lymph nodes, spleen and/or liver should be recorded in the source document and CRF.
- **B symptoms** including fever greater than 38°C, drenching night sweats, and unintentional weight loss of > 10% of normal body weight over a period of 6 months or less.
- **Body weight** will be measured.
- **Vital signs** will include blood pressure, pulse, and body temperature.
- **ECOG Performance Status** will be scored according to Table 11.
- **12-lead electrocardiogram** will be recorded (only at EOT-D).

Safety laboratory tests will be performed at the designated central laboratory; however, in urgent cases, local laboratory results may be used to guide clinical decisions and dose modifications, and, that data must be submitted to Celgene in the CRF, and whenever possible, a concurrent sample should be sent to the Central Laboratory.

Refer to the Laboratory Manual for sample handling, storage, and shipment instructions.

- **Complete blood count with absolute differential** will include hematocrit, hemoglobin, WBC with differential, and platelet count.
- **Clinical chemistry and other laboratory tests** will include albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, bilirubin (total, direct, and indirect), calcium,

chloride, creatinine, glucose, phosphorous, potassium, sodium, total protein, serum urea/ BUN and uric acid.

- **Lactic Dehydrogenase** will be tested.
- **Gamma glutamyl transferase, amylase, and lipase** will be tested.
- **Thyroid function tests** will include TSH, if TSH is abnormal, then reflex testing for fT4 and fT3 (only at EOT-D).
- **Coagulation tests** will include prothrombin time, international normalized ratio (INR) and partial thromboplastin time (PTT or activated PTT) (only at EOT-D).
- **Quantitative immunoglobulins** including IgG, IgA and IgM will be measured (only at EOT-D).
- **Immunogenicity, and biomarker blood sample(s) and tumor samples** will be collected as outlined in Sections 6.6, 6.7, and 6.8 (only at EOT-D).
- **Urinalysis** (a urine dipstick may be used) will include color, appearance, specific gravity, pH, glucose, ketones, blood, bilirubin, and protein. A microscopic examination will be performed if urinalysis result is abnormal.
- **Pregnancy testing** is required for all FCBP subjects. A urine (or serum) pregnancy test (with a sensitivity of at least 25 mIU/mL) will be performed at EOT and 28 days after the last dose of study treatment and 90 days after the last dose of durvalumab.
- **Pregnancy testing for FCBP subjects with irregular menstrual cycles receiving lenalidomide** (applies to all subjects **in Arm A** and subjects in **Arm D** who will receive **subsequent lenalidomide treatment** at the time of progression): A urine (or serum) pregnancy test (with a sensitivity of at least 25 mIU/mL) will be performed at EOT, 14 and 28 days after the last dose of lenalidomide.
- **Lenalidomide Counseling** (applies to all subjects in Arm A and subjects in Arm D who will receive additional lenalidomide treatment at the time of progression): must be conducted. Please consult the Lenalidomide Pregnancy Prevention Risk Management Plan (Appendix F) for details.
- **Efficacy assessments for lymphoma and CLL** (including contrast-enhanced CT scans, FDG-PET-CT, bone marrow biopsy and aspirate, and immunophenotyping of blood for circulating CLL cells by multiparameter flow cytometry) are described in detail in Section 6.4.
- **Interactive response technology** registration (refer to the IRT Manual).
- **Survival status** will be assessed.
- **Subsequent antilymphoma/anticancer treatments status** information will be collected.

6.3. Follow-up Period

6.3.1. Safety Follow-up

All subjects will be followed for AEs (including SAEs and SPMs) and concomitant medications/ procedures for 90 days after the last dose of durvalumab or 28 days after the last dose of other study treatment(s), whichever occurs later. Physical examination for lymphadenopathy and organomegaly, B symptoms, vital signs, CBC with differential, biochemistry including LDH test, thyroid function tests (TSH, if TSH is abnormal, then reflex testing for fT4 and fT3), coagulation, and pregnancy test will be performed according to the Table of Events in Section 5.

The subjects who have received lenalidomide (ie, Arm A or subjects or Arm D who have received lenalidomide at the time of progression) will be followed for SPM for up to five years from the last subject's first lenalidomide dose. Once the subjects complete the efficacy follow-up described below, the SPM follow up may be via telephone and not require site visit.

6.3.2. Efficacy (Long Term) Follow-Up

The Follow-up Period begins upon all study treatment discontinuation or completion as per protocol. This includes subjects who complete the full course of treatment, who discontinue treatment due to progression or toxicity, as well as those who discontinue before progression to pursue a new antilymphoma/CLL therapy.

Subjects will be followed for first progression, subsequent antilymphoma/CLL therapy, and overall survival. Therefore, efficacy assessments will continue at the protocol specified time points until disease progression, withdrawal of ICF, subsequent antilymphoma/CLL treatment, or up to 24 months from subject's last durvalumab dose. In addition, physical examination for lymphadenopathy and organomegaly, and CBC with differential and biochemistry including LDH test, will be repeated at the same time with the efficacy assessments according to the schedule described in Section 6.4.

Following the first documented progression, subjects will be followed for subsequent antilymphoma/CLL therapy and overall survival every 6 months until withdrawal of ICF, or up to 24 months from the subject's last durvalumab dose. This follow-up may be via telephone and not require site visit.

Following completion or discontinuation of durvalumab treatment per protocol for all subjects and completion of the primary analysis (data cutoff date 06 Mar 2019), subjects are no longer required to be followed for disease progression, subsequent antilymphoma/CLL therapy, and overall survival. Follow-up procedures, efficacy assessments, central labs, imaging, and survival data will no longer be collected in the case report forms (CRFs).

In Arm B, subjects receiving benefit from ibrutinib may continue to receive ibrutinib on-study per investigator's medical judgement or discontinue study to receive ibrutinib commercially as standard of care treatment (off-study). Subjects who continue ibrutinib on-study will be treated per investigator's medical judgement and in accordance with standard of care.

6.4. Efficacy Assessments

Efficacy response assessment for this study will be based on:

- Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson, 2014) (Appendix B) for subjects with **lymphoma**.
- IWCLL Response Criteria for CLL (Hallek, 2008; Hallek, 2012; Hallek, 2013) (Appendix C) for subjects with **CLL**.

The following efficacy assessments will be performed at scheduled intervals throughout the study as described in the Table of Events in Section 5.

Scans previously acquired as standard of care within 28 days prior to Cycle 1 Day 1 may be used to fulfill the Screening requirement. Fields missing from archival scans may be imaged separately during Screening and the complete set of scans may be used together to fulfill Screening requirements.

In this study, all tumor assessments will be performed by the investigator. There is no Central Radiology. However, tumor assessment data including images should be made available to the medical monitor or designee upon request. Once a subject has experienced confirmed progression, no further scans are required.

6.4.1. Efficacy Assessments in Lymphoma

For lymphoma, disease response to treatment is determined by the Lugano Classification including a careful review of imaging and laboratory studies and clinical findings.

Integrated PET-CT is preferred for response assessment of FDG-avid lymphomas (eg, DLBCL, HL, FL, transformed large cell lymphoma, Richter's transformation, PMBCL, T-cell/histiocyte rich large B-cell lymphoma, or ALK-positive large B-cell lymphoma), while dedicated CT scan alone is preferred for FDG-non-avid and variably FDG-avid histologies (eg, CLL/SLL, MZL).

6.4.1.1. CT Scans of the Neck, Chest, Abdomen, and Pelvis (Lymphoma)

Contrast-enhanced CT scan alone is the primary modality for baseline staging and response assessment of FDG-non-avid and variably FDG-avid histologies. Magnetic resonance imaging may be used only when CT with contrast is medically contraindicated or when the frequency of CT scans exceeds local standards. Ultrasound is not an acceptable imaging modality for this study.

The same imaging modality (eg, CT or MRI) and technique (eg, use of contract, slice thickness for scans) should be used throughout the study.

The CT scan will be performed at:

- Screening (within 28 days of Cycle 1 Day 1);
- Cycles 4, 7, and 10 Day 1 (± 7 days);
- End of durvalumab treatment (EOT-D)/Cycle 14 Day 1 (± 7 days); and
- Every 6 cycles/months (± 7 days) thereafter.

Following completion of treatment or discontinuation treatment for any reason other than disease progression, the CT scan assessment will continue until disease progression, subsequent antilymphoma/CLL treatment or withdrawal of consent in the Follow-up period (ie, up to 24

months from the subject's last durvalumab dose) based on the schedule above. Unscheduled tests may be ordered at any time as clinically indicated.

Following completion of the primary analysis (data cutoff date 06 Mar 2019), CT scan assessments are no longer required to be collected in the CRFs. Subjects who continue to receive ibrutinib on-study will be treated per investigator's medical judgement.

6.4.1.2. FDG-PET-CT Scan (Whole Body) (Lymphoma)

Separate PET scans using 18F-fluorodeoxyglucose (18F-FDG) plus separate dedicated CT scans or integrated FDG-PET-CT are preferred for FDG-avid lymphomas (eg, DLBCL, HL, FL, transformed large cell lymphoma, Richter's transformation, PMBCL, T-cell/histiocyte rich large B-cell lymphoma, or ALK-positive large B-cell lymphoma).

FDG-PET-CT scans should be performed at:

- Screening (strongly recommended) (within 28 days of Cycle 1 Day 1) Any time during the study (within 14 days following demonstration of nodal CR by CT scan alone) to confirm CR by CT scan alone

Interim dedicated CT scans will be done at Cycles 4, 7, 10, or Cycle 14 Day 1/end of durvalumab treatment (EOT-D)/ (± 7 days) (please see Section 6.4.1.1).

FDG-PET-CT scans are optional at all other response assessment time points.

A positive PET scan is determined visually by comparing the intensity of the suspected area of malignancy to the intensity of activity in the mediastinal blood pool (please see Appendix B).

A dedicated contrast-enhanced CT scan may be required in addition to the FDG-PET-CT to define the extent of disease in special situations, such as in the setting of lymphadenopathy close to bowel or if there is compression or thrombosis of blood vessels.

6.4.1.3. Bone Marrow Biopsy and Aspirate (Lymphoma)

Bone marrow biopsy (BMB) and aspirate to evaluate marrow disease (at site's local pathology laboratory) and biomarker and/or MRD studies in FL and MCL (at designated analytical laboratories) will be performed at:

- Screening (within 12 weeks of Cycle 1 Day 1) in subjects with suspected bone marrow involvement by lymphoma as per investigator's discretion;
- Any time necessary to confirm CR (within 28 days of meeting the criteria for nodal CR by CT (non-FDG-avid histologies) or FDG-PET-CT (in FDG-avid histologies) scan alone except in subjects with no evidence of lymphomatous marrow involvement performed during screening.

Note: If an FDG-PET-CT is performed and confirms FDG-negative CR, no BMB and/or aspirate is required for subjects with aggressive lymphoma histologies (eg, DLBCL, HL).

If an archival specimen is not available or is not acceptable, a rebiopsy is required prior to Cycle 1 Day 1.

6.4.1.4. Minimal Residual Disease (MCL and FL)

Minimal residual disease will be assessed in subjects with MCL and FL by the designated central analytical laboratory.

The MRD in MCL will be monitored for clearing of CD19+, CD5+, and CD23- MCL cells by sensitive multiparameter flow cytometry.

The MRD in FL will be monitored for Bcl-2 by polymerase chain reaction (PCR) to see if there are any residual cells containing 14; 18 translocations.

From subjects with MCL or FL:

- Collect and submit a pretreatment blood sample for MRD on Cycle 1 Day 1
- Confirm PET-negative CR and then:
  - In subjects with no evidence of lymphomatous marrow involvement documented at screening:
    - Collect and submit a blood sample and a bone marrow aspirate sample for MRD assessment (within 28 days of meeting the criteria for PET-negative CR)
    - Collect and submit repeat blood and bone marrow aspirate samples (as available) every 3 cycles while on treatment and every 6 months in the Follow-up Period until evidence of clinical disease progression during the study
  - In subjects with lymphomatous bone marrow involvement documented or no bone marrow biopsy performed at Screening:
    - Collect and submit bone marrow biopsy and aspirate samples to site's local pathology laboratory to confirm no lymphomatous marrow involvement (within 28 days of meeting the criteria for PET-negative CR) (see Section 6.4.1.3). At the same time, collect and submit a blood and bone marrow aspirate sample for MRD assessment.
    - If CR is confirmed by no evidence of lymphomatous bone marrow involvement by site's local pathology assessment, then collect and submit repeat blood and bone marrow samples (as available) every 3 cycles while on treatment and every 6 months in the Follow-up Period until evidence of clinical disease progression during the study
    - If CR based on imaging is not confirmed by BM examination, then no additional MRD samples will be collected.

6.4.2. Efficacy Assessments in CLL

For CLL, disease response to treatment is determined based on the IWCLL Response Criteria including a careful review of laboratory and imaging studies as well as clinical findings.

6.4.2.1. CT Scans of the Neck, Chest, Abdomen, and Pelvis (CLL)

Contrast-enhanced CT scans of the neck, chest, abdomen, and pelvis must be performed for all subjects with CLL. Magnetic resonance imaging may be used only when CT with contrast is medically contraindicated or when the frequency of CT scans exceeds local standards. The same imaging modality should be used throughout the study. Ultrasound is not an acceptable imaging modality for this study.

The same imaging modality (eg, CT or MRI) and technique (eg, use of contract, slice thickness for scans) should be used throughout the study.

The CT scans will be performed at:

- Screening (within 28 days of Cycle 1 Day 1);
- Cycle 7 Day 1 (± 7 days) is required for only affected regions with abnormal findings at baseline; and
- Any time necessary to confirm suspected CR (by clinical [physical examination or symptoms] and CBC-based) (within 8 weeks after clinical and CBC-based CR) (**recommended** unless its frequency exceeds local standards).

Additional CT scans are allowed as clinically indicated until disease progression, subsequent antilymphoma/CLL treatment, or withdrawal of consent in the Follow-up Period.

Unscheduled tests may be ordered at any time as clinically indicated.

6.4.2.2. Bone Marrow Biopsy and Aspirate (CLL)

Bone marrow biopsy (BMB) and aspirate to evaluate marrow disease (at site's local laboratory) and tumor microenvironment and/or MRD (at designated analytical laboratories) (biomarker analysis; please see Section 6.8) will be performed at:

- Screening;
- Cycles 7 Day 1 (± 7 days);
- End of durvalumab treatment (EOT-D)/Cycle 14 Day 1 (± 7 days);
- Any time necessary to confirm suspected CR (by clinical [physical examination or symptoms], CBC-based, and imaging assessments) (within 12 weeks); and
- To evaluate cytopenia of uncertain cause (as clinically indicated).

6.4.2.3. Minimal Residual Disease (Immunophenotyping of Blood for Circulating CLL Cells by Multiparameter Flow Cytometry) (CLL)

Minimal residual disease will be assessed in subjects with CLL by the designated central analytical laboratory.

From subjects with CLL (excluding SLL):

- Collect and submit a pretreatment blood sample for MRD assessment on Cycle 1 Day 1

- Collect and submit a blood sample for MRD assessment within 14 days of meeting the criteria for suspected CR by clinical, CBC-based, and imaging assessments
- Collect and submit bone marrow biopsy and aspirate samples to site's local pathology laboratory to confirm bone marrow recovery (within 12 weeks of meeting the criteria for suspected CR) (see Section 6.4.2.2). At the same time, collect and submit a blood and bone marrow aspirate sample for MRD assessment.
- Collect and submit repeat blood and bone marrow aspirate samples (as available) every 3 cycles while on treatment and every 6 months in the Follow-up Period from subjects with CR/CRi until evidence of clinical disease progression during the study.

6.5. Safety Assessments

Safety assessments include monitoring for AEs; physical examination; vital signs and body weight measurement; ECOG performance status; HBV screening; hematology (CBC with differential and platelets); serum chemistry; urinalysis; serum immunoglobulins; concomitant medications, therapies, and procedures; pregnancy testing (for FCBP only); and ECG.

Safety assessments will be performed during screening and will be repeated weekly in Cycle 1, bi-weekly in Cycles 2 through 4 in Arms A, B, D or Cycles 2 through 6 in Arm C, and once every 4 weeks thereafter for all arms.

For subjects continuing on ibrutinib, clinic visits will be in accordance with standard of care per the investigator's discretion.

The investigator remains responsible to monitor safety, record adverse events (AEs)/serious adverse events (SAEs)/second primary malignancies(SPMs) in source documents, and report SAEs and SPMs to Celgene Drug Safety.

Adverse event assessment begins when the subject signs the ICF.

Please see Section 10 for definition of AE and SAE.

6.6. Pharmacokinetics

Pharmacokinetic assessments for durvalumab, lenalidomide and ibrutinib are mandatory and will be performed for all subjects enrolled into the study.

If PK samples collected from Phase 1 can achieve PK objective(s), no further PK sampling may be collected in the Phase 2 portion of the study.

On PK sampling days, dosing and sample collection information including dosing date, dosing time (24-hour clock), and actual PK blood sampling time (24-hour clock) should be accurately documented on the appropriate CRF pages.

6.6.1. Pharmacokinetics of Durvalumab (All Arms)

Pharmacokinetic sampling will be performed for all subjects receiving durvalumab (including those subjects in Arm D who will receive additional combination treatment following disease progression). The sampling time points will be as follows:

Table 12: Pharmacokinetic Sample Collection Timepoints (All Arms)

Cycle	Day	Time Point
1	1	Pre-durvalumab infusion (-4 hours to -5 minutes prior to durvalumab dose)
1	1	End of durvalumab infusion (EOI) (± 15 minutes)
1	1	4 hours post EOI (± 1 hour)
1	2	24 hours post EOI (± 8 hours)
1	3	48 hours post EOI (± 8 hours)
1	8	168 hours post EOI (± 24 hours)
1	15	336 hours post EOI (± 24 hours)
1	22	504 hours post EOI (± 24 hours)
2	1	Pre-durvalumab infusion (-4 hours to -5 minutes prior to durvalumab dose)
2	1	End of durvalumab infusion (EOI) (± 15 minutes)
2	1	4 hours post EOI (± 1 hour)

Table 12: Pharmacokinetic Sample Collection Timepoints (All Arms) (Continued)

Cycle	Day	Time Point
2	15	336 hours post EOI (± 24 hours)
4	1	Pre-durvalumab infusion (-4 hours to -5 minutes prior to durvalumab dose)
6	1	Pre-durvalumab infusion (-4 hours to -5 minutes prior to durvalumab dose)
10	1	Pre-durvalumab infusion (-4 hours to -5 minutes prior to durvalumab dose)
14/EOT-D	1	Pre-durvalumab infusion (-4 hours to -5 minutes prior to durvalumab dose)

Abbreviation: EOI = end of infusion; EOT-D = end of treatment of durvalumab.

6.6.2. Pharmacokinetics of Lenalidomide (Arm A Only)

PK sampling will be performed for all subjects enrolled in Arm A receiving lenalidomide (excluding those subjects in Arm D who will receive lenalidomide as additional add-on combination treatment following disease progression). The sampling time points will be as follows:

Table 13: Pharmacokinetic Sample Collection Timepoints (Arm A Only)

Cycle	Day	Time Point
1	1	Pre-lenalidomide (-4 hours to -5 minutes prior to lenalidomide dose)
1	1	1 hour (± 10 minutes) post-lenalidomide dose
1	1	2 hours (± 10 minutes) post-lenalidomide dose
1	1	4 hours (± 10 minutes) post-lenalidomide dose
1	2	24 hours (± 2 hours) post-lenalidomide dose
1	15	Pre-lenalidomide 4 hours to -5 minutes prior to lenalidomide dose)

1	15	1 hour (± 10 minutes) post-lenalidomide dose
1	15	2 hours (± 10 minutes) post-lenalidomide dose
1	15	4 hours (± 10 minutes) post-lenalidomide dose

6.6.3. Pharmacokinetics of Ibrutinib (Arm B only)

PK sampling will be performed for all subjects enrolled in Arm B receiving ibrutinib (excluding those subjects in Arm D who will receive ibrutinib as additional add-on combination treatment following their infusion). The sampling time points will be as follows:

Table 14: Pharmacokinetic Sample Collection Timepoints (Arm B only)

Cycle	Day	Time point
1	1	Pre-ibrutinib (-4 hours to -5 minutes prior to ibrutinib dose)
1	1	1 hour (± 10 minutes) post-ibrutinib dose
1	1	2 hours (± 10 minutes) post-ibrutinib dose

Table 14: Pharmacokinetic Sample Collection Timepoints (Arm B only) (Continued)

Cycle	Day	Time point
1	1	4 hours (± 10 minutes) post-ibrutinib dose
1	2	24 hours (±2 hours) post-ibrutinib dose
1	15	Pre-ibrutinib (-4 hours to -5 minutes prior to ibrutinib dose)
1	15	1 hour (± 10 minutes) post-ibrutinib dose
1	15	2 hours (± 10 minutes) post-ibrutinib dose
1	15	4 hours (± 10 minutes) post-ibrutinib dose

6.7. Immunogenicity

Immunogenicity samples will be collected from all subjects receiving durvalumab (all 4 treatment arms - including those subjects in Arm D who will receive additional add-on combination treatment following disease progression).

On immunogenicity sampling days, dosing and sample collection information including dosing date, dosing time (24-hour clock), and actual immunogenicity blood sampling time (24 hour clock) should be accurately documented on the appropriate CRF pages.

Samples will be stored, and ADA will be explored using the stored samples. The sampling time points will be as follows:

Table 15: Immunogenicity Sample Collection Timepoints

Cycle	Day	Time Point
1	1	Pre-durvalumab infusion
2	1	Pre-durvalumab infusion

Cycle	Day	Time Point
4	1	Pre-durvalumab infusion
6	1	Pre-durvalumab infusion
10	1	Pre-durvalumab infusion
14/EOT-D	1	Pre-durvalumab infusion

Abbreviations: EOT-D = end of treatment of durvalumab.

6.8. Biomarkers, Pharmacodynamics, Pharmacogenomics

Saliva, blood, bone marrow biopsy and aspirate (subjects with CLL and, if available, lymphoma), and tumor tissue biopsies will be collected and analyzed to evaluate protein, nucleic acid and cellular biomarkers that relate to durvalumab, combination treatment, and disease according to the schedule presented in Table 7, Table 8, Table 9, and Table 10.

6.8.1. Tumor Tissue Biopsy for Biomarker Assessments (Lymphoma)

The collection of tumor tissue is mandatory in subjects with lymphoma. The tumor biopsy will be collected either by tumor excision, incision, or multiple core needles (4 passages preferred) and submitted to the Central Laboratory in order to evaluate tumor microenvironment as well as to identify potential predictive/Pd biomarkers.

Table 16: Tumor Tissue Biopsy Collection Timepoints for Biomarkers

Timepoints	Window	Requirement
Screening[a]	Within 28 days of Cycle 1 Day 1	Mandatory
Any time during Cycle 2	-	Strongly recommended
At the time of PD in subject who achieved objective responses (CR/PR)	Within 14 days of documented PD	Mandatory
Any available archival sample collected prior to study entry or unscheduled sample collected during the study	-	If available, submit to the Central Laboratory (strongly recommended)

Abbreviations: CR = complete response, PD = progressive disease, PR = partial response.

[a] An archival lymph node/tumor formalin fixed paraffin embedded (FFPE) biopsy sample acquired by a surgical or core needle biopsy within 3 months prior to signing informed consent and with no intervening treatment after the biopsy may be acceptable for enrollment of a subject with **poorly accessible tumor following the discussion with the sponsor's medical monitor**. **The discussion must take place prior to Screening (strongly recommended) or during Screening.**

In addition, it is strongly recommended to submit to the Central Laboratory any archival tumor biopsy samples collected prior to study entry or during the study at time points other than described above for biomarker analysis.

Fine needle aspiration is not sufficient as a source of tumor biopsy material.

Refer to the Laboratory Manual for sample collection and processing instructions.

6.8.2. Bone Marrow Biopsy and Aspirate for Biomarker Assessments

Bone marrow biopsy and aspirate samples will be collected from subjects with CLL and from subjects with lymphoma (as available) to investigate tumor-immune microenvironment and other molecular markers associated with disease or response at the following time points below. The samples will be analyzed at designated analytical laboratories for biomarkers.

The assessments for bone marrow disease should be performed at site's local pathology laboratories.

Table 17: Bone Marrow Biopsy and Aspirate Collection Timepoints for Biomarkers - CLL

Timepoints	Window	Requirement
Screening	Within 28 days of Cycle 1 Day 1	Mandatory
Cycle 7 Day 1	± 7 days	Mandatory
End of durvalumab treatment (EOT-D)/Cycle 14 Day 1	± 7 days	Mandatory

Table 17: Bone Marrow Biopsy and Aspirate Collection Timepoints for Biomarkers - CLL (Continued)

Timepoints	Window	Requirement
To confirm suspected CR (by clinical, laboratory [including peripheral blood flow-negativity], and imaging assessments)	Within 12 weeks of suspected CR	Mandatory
Any available archival sample collected prior to study entry or unscheduled sample collected during the study	-	If available, submit to the Central Laboratory (strongly recommended)

Abbreviations: CR = complete response, EOT-D = end of treatment – durvalumab

Table 18: Bone Marrow Biopsy and Aspirate Collection Timepoints for Biomarkers - Lymphoma

Timepoints	Window	Requirement
Screening	Within 12 weeks of Cycle 1 Day 1	If collected, submit to the Central Laboratory
Nodal CR by CT or FDG-PET-CT alone	Within 4 weeks of nodal CR	If collected, submit to the Central Laboratory
Any available archival sample collected prior to study entry or unscheduled sample collected during the study	-	If available, submit to the Central Laboratory (strongly recommended)

Abbreviations: CR = complete response; CT= computerized tomography; FDG= fluorodeoxyglucose; PET= positron emission tomography

In addition, it is strongly recommended to submit to the Central Laboratory any archival bone marrow biopsy samples collected prior to study entry or during the study at time points other than described above for biomarker analysis.

6.8.3. Saliva and Blood Samples for Biomarker Assessments

A saliva sample for biomarkers will be collected at Screening.

Blood samples for biomarkers will be collected to analyze Pd/predictive/disease markers at the following time points:

- Screening;
- Cycle 1: Days 1, 8, and 15 (all predose, as applicable)
- Cycle 2: Days 1 and 15 (all predose, as applicable)
- Cycle 3: Day 15 (predose, as applicable)
- Cycle 4: Day 15 (predose, as applicable)
- EOT-D/Cycle 14 Day 1 (predose, as applicable)

The type of samples which should be collected on each time point is listed in the Table of Events in Section 5.

Please refer to Sections 6.4.1.4 and 6.4.2.3 for the MRD monitoring in MCL, FL, and CLL.

Details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

Investigational product supply will be managed by IRT. All IPs (except local IFRT) must be stored in accordance with the product label in a secured area to prevent unauthorized access. The IP (except local IFRT) will be labeled as per local regulations.

7.1.1. Durvalumab

Durvalumab (MEDI4736) will be supplied by Celgene in single use vials in single count cartons. Each 10R vial will be supplied as a vialed liquid solution containing 500 mg (nominal) of durvalumab at a concentration of 50 mg/mL. Durvalumab should be stored in accordance with the product label.

- Sites will supply IV infusion bags with dilution solution and infusion lines with appropriate filters. IV infusion bags of normal saline (0.9% [w/v] sodium chloride injection, 250 mL size) or dextrose (5% [w/v] dextrose injection, 250 mL). Saline or dextrose bags must be latex-free and can be made of polypropylene, polyethylene, polyolefin copolymers, or polyvinyl chloride. Infusion lines should contain a 0.2 - 0.22 μm in-line filter.

Since the compatibility of durvalumab with other IV medications and solutions, other than normal saline and dextrose, is not known, the durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered.

For additional information on supplies, preparation and storage, please refer to the Pharmacy Manual.

7.1.2. Lenalidomide

Lenalidomide will be supplied by Celgene in appropriate strengths for oral administration. Investigational product will be supplied as labeled blister cards. Lenalidomide should be stored in accordance to the product label. Lenalidomide should be stored in accordance to the product label.

No new subjects are to be treated in combination with durvalumab plus lenalidomide with or without rituximab (Arm A). 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.

For additional information on preparation and storage, please refer to the Pharmacy Manual.

7.1.3. Rituximab

Rituximab will be supplied outside the US by Celgene and labeled appropriately as investigational material for the study. For the US, rituximab will not be supplied by the sponsor; instead, it will be obtained according to local clinical study agreement and in accordance with local guidelines.

Depending on local guidelines, this protocol allows the use of:

- Rituximab IV standard infusion time
- Rituximab IV biosimilars
- Rituximab subcutaneous (1400 mg/11.7 mL fixed dose in FL or DLBCL; and 1400 mg/11.7 mL fixed dose at Cycle 1 followed by 1600 mg/13.4 mL fixed dose at Cycle 2 onward in CLL/SLL)

It is acceptable to use dose banding for rituximab or BSA capping at 2.0 mg/m^2 as per local practice.

Please refer to the locally approved rituximab label or Pharmacy Manual for preparation, administration, or storage information.

For additional information on preparation and storage, please refer to the Pharmacy Manual.

7.1.4. Ibrutinib

Ibrutinib will be supplied outside the US by Celgene and labeled appropriately as investigational material for the study. For the US, ibrutinib will not be supplied by the sponsor; instead it will be obtained according to local clinical study agreement and in accordance with local guidelines.

Ibrutinib will be supplied as 140 mg capsules or 140 mg tablets.

For additional information on preparation and storage, please refer to the Pharmacy Manual.

7.1.5. Bendamustine

Bendamustine will be supplied outside the US by Celgene and labeled appropriately as investigational material for the study. For the US, bendamustine will not be supplied for its approved indications by the sponsor; instead it will be obtained according to the local clinical study agreement and in accordance with local guidelines.

Bendamustine will be supplied in appropriate strengths in vial as injection solution and/or lyophilized powder for injection.

For additional information on preparation and storage, please refer to the Pharmacy Manual.

7.1.6. Local Involved Field Radiation Therapy

Local involved field radiation (IFRT) therapy may be added based on 2 Gy on each of 2 consecutive days to one tumor site in subjects who have with at least 1 measurable lesion (> 1.5 cm and outside of the involved field that will be irradiated) at the time of disease progression in Arm D (durvalumab monotherapy). This therapy will be provided at the sites.

Following IFRT, the subject will receive monthly durvalumab doses for up to 6 cycles based on investigator's medical judgment.

7.2. Treatment Administration and Schedule

Subjects who are eligible will be assigned to one of the following arms (depending on the study part):

- **Arm A:** durvalumab and lenalidomide ± rituximab **(this arm is discontinued to the enrollment of new subjects; subjects already enrolled and treated who are**

receiving clinical benefit, based on the discretion of the investigator, may continue study treatment after being reconsented)

- **Arm B:** durvalumab and ibrutinib
- **Arm C:** durvalumab and rituximab ± bendamustine
- **Arm D:** durvalumab (monotherapy)

7.2.1. Dose Finding Cohorts (Phase 1)

The following dose finding cohorts are planned.

Table 19: Planned Dose Finding Cohorts

Treatment Arm	Eligible Histologies
Arm A[a] **(discontinued to the enrollment of new subjects)**	R/R B-Cell NHL
Arm B	R/R B-cell NHL R/R CLL
Arm C	R/R B-cell NHL R/R CLL
Arm D	No dose finding cohort

Abbreviations: CLL = chronic lymphocytic leukemia; NHL = non-hodgkin lymphoma; R/R = relapsed/refractory, SLL = small lymphocytic lymphoma.
[a] Arm A will exclude the subjects with CLL or SLL.

7.2.1.1. Arm A: Durvalumab and Lenalidomide ± Rituximab (Discontinued to the Enrollment of New Subjects)

Subjects assigned to Arm A will receive:

- Durvalumab (IV) infusion on Day 1 of Cycles 1 through 13 (ie, 12 months);
- Lenalidomide (PO) once daily on Days 1 to 21 (inclusive) of:
  - Cycles 1 through 13 in indolent NHL (ie, FL or MZL) or
  - All cycles of treatment period until disease progression, unacceptable toxicity, or discontinuation for any other reason in aggressive NHL (eg, DLBCL); and
- Rituximab (IV) infusion:
  - Rituximab Schedule 1 (dose levels 2 and -1B): on **Days 2**, 8, 15 and 22 of Cycle 1 and on **Day 1** from Cycles 2 through 5
  - Rituximab Schedule 2 (dose levels -2 and -3): on **Day 2** of Cycle 1 and on **Day 1** from Cycles 2 through 8

All treatment cycles are 28 days. Durvalumab infusion will be administered before any other IP on the days which more than one investigational treatment should be given (eg, Day 1 of Cycles

1 through 13), and then lenalidomide administration and rituximab infusion are recommended to follow, respectively.

Initial cohorts of 3 subjects will be treated at dose levels listed on Table 20. If one DLT occurs in the first 3-subject cohort at a dose level during the DLT observation period (ie, from the time of the first IP dose through completion of Cycle 1), that cohort will enroll up to 6 subjects. Even in the absence of a DLT, additional subjects may be evaluated within a dose cohort if recommended by the SRC to adequately evaluate the safety or treatment effects of durvalumab in combination with lenalidomide and/or rituximab (depending on dose level).

If dose level 1 is found to be the NTD, dose level -1A and dose level -1B may be explored at the discretion of the SRC. The SRC may decide to explore subsequent dose levels if dose level 2 is found to be NTD.

The dose finding flow in Arm A is illustrated in Figure 4.

Table 20: Dose Finding: Arm A Dose Levels (Discontinued to the Enrollment of New Subjects)

Dose Level	Durvalumab (IV)	Lenalidomide (PO)	Rituximab (IV) (Schedule 1)	Rituximab (IV) (Schedule 2)
-3	1500 mg	10 mg	-	375 mg/m^2
-2	1500 mg	15 mg	-	375 mg/m^2
-1B	1500 mg	10 mg	375 mg/m^2	-
-1A	1500 mg	10 mg	-	-
1 (starting)	1500 mg	20 mg	-	-
2	1500 mg	20 mg	375 mg/m^2	-
Schedule (28-day cycle)	Day 1 of Cycles 1-13	Once daily (QD) on Days 1-21 -Up to 12 months in FL or MZL -Up to disease progression in aggressive histologies	Weekly × 4 in Cycle 1 (Days 2, 8 15, & 22) and Day 1 of Cycles 2-5	Day 2 of Cycle 1 and Day 1 of Cycles 2- 8

Abbreviations: IV = intravenous; PO = orally; QD = once daily.

7.2.1.1.1. Arm A: Durvalumab Administration (Discontinued to the Enrollment of New Subjects)

Durvalumab at a fixed dose of 1500 mg will be administered as an IV infusion (250 mL) over approximately one hour in duration on Day 1 of Cycles 1 through 13.

Durvalumab infusion will be administered before any other IP on Day 1. Please refer to the Pharmacy Manual for dose preparation and administration guidance.

7.2.1.1.1.1. Durvalumab Dose Administration

Durvalumab must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein or central line. Please see the Pharmacy Manual for further details.

7.2.1.1.1.2. Monitoring of Dose Administration

Vitals signs will be monitored before, during and after infusion at the times specified in the Schedule of Assessment. Subjects are monitored (pulse rate, blood pressure, and body temperature) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of durvalumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and reinitiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤ Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen/paracetamol and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, durvalumab will be discontinued. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature, with maximum total time at room temperature not exceeding 4 hours (otherwise requires new infusion preparation).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

7.2.1.1.2. Arm A: Lenalidomide Administration (Discontinued to the Enrollment of New Subjects)

Lenalidomide (PO) will be administered after the durvalumab infusions on the days (eg, Day 1 of Cycles 1 through 13) when more than one IP should be given.

Lenalidomide 10 mg, 15 mg, or 20 mg dose (depending on dose level in the dose finding part or renal function in the dose confirmation and expansion parts) should be taken orally once daily, at approximately the same time each day. There is no requirement for taking lenalidomide with or without food, or with or without certain types of foods or liquids.

Lenalidomide doses will be taken from Days 1 through 21 of a 28-day cycle. A 7-day rest period is required. A rest period may be extended due to toxicity as needed.

Lenalidomide dose adjustment based on subject's creatinine clearance in case of starting dose of lenalidomide 15 mg or 20 mg (the dose confirmation and expansion parts only):

Lenalidomide dosing will be based on subject's creatinine clearance calculated using the Cockcroft-Gault formula using actual body weight. This calculation will be performed by the Central Laboratory based on actual body weight.

- Subjects who have a creatinine clearance ≥ 60 mL/min (≥ 1.0 mL/sec) will receive lenalidomide at a dose of **15 mg** or **20 mg** (depending on the dose level assigned) once daily on Days 1 through 21 of each 28-day cycle. The subjects eligible for **the dose finding part** must have a creatinine clearance ≥ 60 mL/min (≥ 1.0 mL/sec).
- Subjects with moderate renal insufficiency (creatinine clearance ≥ 40 mL/min but < 60 mL/min; ≥ 0.5 mL/sec but < 1.0 mL/sec) will be eligible for **the dose confirmation and expansion parts only**. In this case, a lower starting dose of lenalidomide of **10 mg** once daily will be given on Days 1 through 21 of a 28-day cycle. in Cycle 1 and in Cycle 2. If the subject remains free of IP-related Grade 3 or 4 toxicities for at least 2 cycles, the dose may be increased to **15 mg** once daily on Days 1 to 21 of a 28-day cycle at the discretion of the treating physician from Cycle 3 onwards.

If subjects miss a dose of lenalidomide and it is within 12 hours of their normal dosing time, the subjects should be instructed to make up the missed dose, and to then take their next dose according to their regular schedule. Lenalidomide concentration is low at 12 hours post dose, therefore, making up a missed dose and then resuming regular dosing with ≥ 12-hour interval between 2 doses will not cause considerable drug accumulation.

7.2.1.1.3. Arm A: Rituximab Administration (Discontinued to the Enrollment of New Subjects)

Rituximab will be administered at 375 mg/m^2 every week in Cycle 1 (Days 2, 8, 15, 22) and on Day 1 of every 28-day cycle from Cycles 2 through 5.

All dosage calculations for rituximab will be based on the subject's BSA, using actual weight for calculations. This will be determined during the Screening Visit or on the first day of IP administration in Cycle 1 and will be calculated using the subject's height and weight according to local pharmacy practice.

It is up to the pharmacist's and investigator's discretion whether BSA will be recalculated prior to preparing every cycle of rituximab, or whether the BSA calculated prior to the first dose of rituximab will be used throughout the study. If BSA is to be recalculated, the same calculation method should be used throughout the study per subject.

Preparation, infusion rate, dose modification, and premedication should be performed according to the locally approved rituximab prescribing information.

7.2.1.2. Arm B: Durvalumab and Ibrutinib

Subjects assigned to Arm B will receive:

- Durvalumab (IV) infusion on Day 1 of Cycles 1 through 13
- Ibrutinib (PO) continuous once daily until disease progression, unacceptable toxicity, starts new therapy, or discontinuation for any other reason, ie, subject withdraws consent or discontinues per investigator's discretion.

All treatment cycles are 28 days. Durvalumab infusion will be administered before ibrutinib on the days which both IPs should be given.

Initial cohorts of 3 subjects will be treated at dose levels listed in Table 21. If one DLT occurs in the first 3-subject cohort at a dose level during the DLT observation period (ie, from the time of first IP dose through completion of Cycle 1), that cohort will enroll up to 6 subjects. Even in the absence of a DLT, additional subjects may be evaluated within a dose cohort if recommended by the SRC to adequately evaluate the safety or treatment effects of durvalumab in combination with ibrutinib. If dose level 1 is found to be the NTD, dose level -1 may be explored at the discretion of the SRC. Dose level 2 will enroll only the subjects with NHL.

The dose finding flow is illustrated Figure 5.

Table 21: Dose Finding: Arm B Dose Levels

Dose Level	Durvalumab (IV)	Ibrutinib (PO)
-1	1500 mg	280 mg
1 (starting)	1500 mg	420 mg
2	1500 mg	560 mg **(only in NHL)**
Schedule (28-day cycle)	Day 1 of Cycles 1-13	Once daily on Days 1-28 (QD)

Abbreviations: IV = intravenous; PO = orally; QD = once daily.

7.2.1.2.1. Durvalumab Administration

Please see Section 7.2.1.1.1.

7.2.1.2.2. Ibrutinib Administration

Ibrutinib (PO) will be administered after the durvalumab infusion on the days (eg, Day 1 of Cycles 1 through 13) in which both investigational treatments should be given.

Ibrutinib, depending on dose level, 280 mg (2 × 140 mg capsules/tablets), 420 mg (3 × 140 mg capsules/tablets; **maximum allowed dose in CLL**) or 560 mg (4 × 140 mg capsules/tablets; **only in NHL**) is administered orally once daily with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. Tablets should be swallowed intact and subjects should not attempt to crush or dissolve them in water.

If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules or tablets to make up the missed dose.

Ibrutinib dosing is continuous (without interruption) throughout the Treatment Period. If Day 1 durvalumab dosing is delayed for toxicity that does not require ibrutinib to be held for toxicity, ibrutinib dosing should continue. If Day 1 (of any Cycle) durvalumab infusion is delayed due to scheduling delays, ibrutinib dosing should continue.

7.2.1.3. Arm C: Durvalumab and Rituximab ± Bendamustine

Subjects assigned to Arm C will receive:

- Durvalumab (IV) infusion on Day 1 of Cycles 1 through 13

- Bendamustine (IV) infusion on Days 1 and 2 of Cycles 1 through 6
- Rituximab (IV) infusion on Day 2 Cycles 1 through 6
  - **In NHL,** rituximab dose is 375 mg/m^2 in all cycles.
  - **In CLL,** rituximab dose is 375 mg/m^2 (Cycle 1; first dose) and 500 mg/m^2 (subsequent doses: Cycle 2 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 as per the investigator's medical judgment. If bendamustine is stopped earlier than 6 cycles, rituximab may be continued up to 6 cycles.

All treatment cycles are 28 days. Durvalumab infusion will be administered before bendamustine on the days (eg, Day 1 of Cycles 1 through 6) which more than one investigational treatment should be given, and then bendamustine and rituximab administration are recommended to follow, respectively.

Initial cohorts of 3 subjects will be treated at dose levels listed on Table 22. If one DLT occurs in the first 3-subject cohort at a dose level during the DLT observation period (ie, from the time of first IP dose through completion of Cycle 1), that cohort will enroll up to 6 subjects. Even in the absence of DLT, additional subjects may be evaluated within a dose cohort if recommended by the SRC to adequately evaluate the safety or treatment effects of durvalumab in combination with rituximab and/or bendamustine (depending on dose level). If the dose level 2 is found to be the NTD, dose level -1 may be explored.

The dose finding flow is illustrated in Figure 6.

Table 22: Dose Finding: Arm C Dose Levels

Dose Level	Durvalumab (IV)	Rituximab (IV)[a]	Bendamustine (IV)
1 (starting)	1500 mg	375 mg/m^2	-
2[b]	1500 mg	375 mg/m^2	70 mg/m^2
3	1500 mg	375 mg/m^2	90 mg/m^2 **(only in NHL)**
Schedule	Day 1 of Cycles 1-13	Day 2 of Cycles 1-6	Days 1 and 2 of Cycles 1-6

Abbreviations: IV= intravenous.
[a] In subjects with CLL, rituximab dose is 375 mg/m^2 (first dose; Cycle 1) and 500 mg/m^2 (subsequent doses; Cycle 2 and on).
[b] In subjects with CLL, the maximum allowed dose of bendamustine will be 70 mg/m^2.

7.2.1.3.1. Arm C: Durvalumab Administration

Please see Section 7.2.1.1.1.

7.2.1.3.2. Arm C: Bendamustine Administration

Bendamustine will be administered as a 30-minute IV infusion at a dose of 70 or 90 mg/m^2 **(only in NHL)** (depending on dose level).

All dosage calculations for bendamustine will be based on the subject‘s body surface area (BSA), using actual weight for calculations. This will be determined during Screening or on the first day of IP administration of Cycle 1 and will be calculated using the subject’s height and weight according to local pharmacy practice.

It is up to pharmacist’ and investigator’ discretion whether BSA will be recalculated prior to preparing every cycle of bendamustine, or whether the BSA calculated prior to the first dose of bendamustine will be used throughout the study. If BSA is to be recalculated, the same calculation method should be used throughout the study per subject

The timing of bendamustine on Day 2 should be approximately the same time on Day 1. The preparation and infusion of bendamustine will be according to the locally approved label.

7.2.1.3.3. Arm C: Rituximab Administration

Rituximab will be administered at 375 mg/m^2 to the subjects with NHL and at 375 mg/m^2 (first dose) followed by 500 mg/m^2 (subsequent doses) to the subjects with CLL on Day 2 of every 28-day cycle from Cycles 1 through 6.

All dosage calculations for rituximab will be based on the subject’s BSA, using actual weight for calculations. This will be determined during Screening or on the first day of IP administration of Cycle 1 and will be calculated using the subject’s height and weight according to local pharmacy practice.

It is up to pharmacist’ and investigator’ discretion whether BSA will be recalculated prior to preparing every cycle of rituximab, or whether the BSA calculated prior to the first dose of rituximab will be used throughout the study. If BSA is to be recalculated, the same calculation method should be used throughout the study per subject.

Preparation, infusion rate, dose modification, premedication and guidance on pregnancy prevention should be performed according to the locally approved label or the Pharmacy Manual.

7.2.1.4. Arm D: Durvalumab Monotherapy

No dose finding cohort is planned. Please see Section 7.2.8.1 for treatment schedule.

7.2.2. Definition of DLT 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 Cycle 1.

7.2.3. Definition of Dose Limiting Toxicity (DLT)

Dose limiting toxicities will be evaluated during the DLT evaluation period for the subjects in the dose finding cohorts. The severity grading of adverse events will be determined according to National Cancer Institute CTCAE Version 4.03 (unless otherwise specified in Section 7.2.10.1).

Dose limiting toxicities are described below:

A DLT will be defined as below:

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

Non-Hematologic DLT

- Any non-hematological 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.

Please see Section 10 for further details on AE reporting.

7.2.4. Definition of a Subject Evaluable for DLTs

Subjects enrolled during **the dose finding part** are considered evaluable for DLTs if they complete the DLT evaluation period specified for each cohort or experience a DLT during the DLT evaluation period.

Non-evaluable subjects may be replaced with another subject at the same dose level. Additional subjects within any dose cohort may be enrolled at the discretion of the SRC.

7.2.5. Definition of Non-Tolerated Dose (NTD)

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

7.2.6. Definition of Maximum Tolerated Dose (MTD)

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.

7.2.6.1. Determination of Preliminary RP2D

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 (as available). The RP2D selected will not exceed the MTD from the dose finding cohorts.

7.2.6.2. Evaluation of Alternate Treatment Schedules

If the SRC determines that toxicity is due to duration or frequency of dosing of any investigational treatment regimen, intermittent dosing schedules not currently specified may be evaluated.

7.2.7. Safety Review Committee

Safety considerations, including but not limited to, decisions to open a new dose level cohort, additional subjects within any dose cohort, or declare a RP2D will be made by the safety review committee (SRC). The SRC membership will be comprised of the sponsor's medical monitor and drug safety physician, a subset of the investigators participating in the study who have sufficient prior experience in early phase studies in CLL or lymphoma. Other study team members (eg, study statistician) may also participate in SRC meetings as needed.

The safety review committee will be informed about any additional safety data available from other durvalumab studies that may affect their decisions and recommendations.

The SRC will continue to review safety data regularly throughout the all phases of the study and make recommendations about study continuation and dose modifications for the IPs (eg, alternate schedule and dose levels not currently specified or split dose) as appropriate.

7.2.8. Dose Confirmation Cohorts (Phase 1)

Once a preliminary RP2D in any dose finding cohort is determined, the relevant dose confirmation cohort may be open for enrollment. Arm D will start directly with the dose confirmation cohorts (no dose finding cohort).

Table 23: Planned Dose Confirmation Cohorts

Treatment Arm	Eligible Histologies[ab]
Arm A[c] **(discontinued to the enrollment of new subjects)**	R/R FL N = 10[d] R/R DLBCL N = 10[d]
Arm B	R/R CLL/SLL N = 10 R/R MCL N =10
Arm C	R/R CLL/SLL N = 10 R/R FL N = 10 R/R DLBCL N = 10
Arm D	R/R CLL/SLL R/R DLBCL R/R FL R/R MCL R/R HL RT (5-10 subjects in each; N = 40)

Abbreviations: N = number of subject; R/R=relapsed/refractory.
[a] Subjects with FL Grade 3b may be enrolled into DLBCL cohorts will be excluded from FL cohorts.
[b] FL cohorts will enroll only subjects with FL Grade 1-3a.
[c] Arm A will exclude subjects with CLL or SLL.

[d] Arm A dose confirmation and dose expansion cohorts are discontinued and will not enroll new subjects.

7.2.8.1. Arm D

Subjects assigned to Arm D will receive:

- Durvalumab (IV) infusion at a fixed dose of 1500 mg, on Day 1 of Cycles 1 through 13. All treatment cycles are 28 days.

The add-on combination treatment with lenalidomide ± rituximab is no longer allowed.*

For subjects in Arm D, at the time of disease progression, the investigator may add study treatments previously investigated once a tolerable dose level is confirmed for that combination (ie, rituximab ± either lenalidomide* or bendamustine; or monotherapy ibrutinib), or local IFRT with durvalumab, if subjects meet the criteria defined in Section 3.1.2.

Subjects who receive a combination agent other than local IFRT will follow the visit schedules and assessments specific to each combination agent (eg, the Arm A visit schedule and assessments starting from Cycle 1 Day 1 will be followed by subjects who receive lenalidomide and rituximab in addition to durvalumab). Those subjects will be treated according to the treatment schedules described for each arm in Section 7.2 based on the investigator's medical judgment.

Subjects who receive local IFRT, 2 Gy on each of 2 consecutive days to one tumor site, as additional therapy will continue to follow the Arm D schedule. Following IFRT, subjects will receive durvalumab for up to an additional 6 cycles (eg, if a subject receives local IFRT following disease progression documented at the end of Cycle 13, he/she may receive 6 additional durvalumab doses, up to Cycle 19), or will complete the remaining scheduled durvalumab doses (ie, 13 cycles) based on the investigator's medical judgment.

The sponsor's medical monitor should be contacted prior to adding a combination agent to durvalumab.

7.2.9. Dose Expansion Cohorts (Phase 2)

The sponsor will decide on dose expansion based on the SRC recommendation and emerging and available clinical and non-clinical data. The following cohorts are anticipated for expansion.

Table 24: Planned Dose Expansion Cohorts

Treatment Arm	Eligible Histologies[ab]
Arm A[c] **(discontinued to the enrollment of new subjects)**	R/R FL N = 15[d] R/R DLBCL N = 15[d]
Arm B	R/R CLL/SLL N = 15 R/R MCL N = 15
Arm C	R/R CLL/SLL N = 15 R/R FL N = 15 R/R DLBCL = 15
Arm D	Not planned

Abbreviations: N = number of subject; R/R = relapsed/refractory.

[a] Subjects with FL Grade 3b may be enrolled into DLBCL cohorts but will be excluded from FL cohorts.
[b] FL cohorts will enroll only subjects with FL Grade 1-3a.
[c] Arm A will exclude subjects with CLL or SLL.
[d] Arm A dose confirmation and dose expansion cohorts are discontinued and will not enroll new subjects.

7.2.10. Dose Modifications (Interruption/Reduction)

Dose modifications are permitted in any cycle for appropriate management of AEs. Dose reductions are allowed for lenalidomide, ibrutinib, and bendamustine. No dose reductions are allowed for durvalumab or rituximab, but treatment may be interrupted or discontinued or infusion rate may be changed at the discretion of the investigator for severe infusion or allergic reactions, or other toxicities.

Dose modifications must be recorded in the Dose Administration CRF.

7.2.10.1. General Dose Modification Guidelines

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.

Dose modifications will not be required for AEs that are clearly not attributable to IPs (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. If an AE occurs, the investigator should assess whether the AE is attributable to any of the IPs. If the AE is attributable to any IP based on the investigator's clinical judgment, then the investigator will follow the dose modification guidelines for that causative IP(s) provided in 7.2.10.7.

Dose interruptions lasting beyond 28 days should be discussed with the sponsor's medical monitor.

If the lowest dose of lenalidomide, ibrutinib, or bendamustine is not tolerated then it will be discontinued from the investigational treatment regimen.

If any combination IP (ie, lenalidomide, ibrutinib, bendamustine, rituximab) is discontinued, subjects may continue on durvalumab with or without another combination IP; this will require discussion and agreement between the sponsor's medical monitor and the investigator.

If durvalumab is discontinued, subjects will be discontinued from all study treatment.

7.2.10.2. Dose Modification for Durvalumab

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing imAEs during the conduct of this study. Potential imAEs may be similar to those seen with the use of ipilimumab, BMS-936558, and BMS-936559 and may include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies (Hodi, 2010; Brahmer, 2012; Topalian, 2013). Subjects should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (eg, infection or disease progression), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy.

In addition to the dose modifications shown in, it is recommended that management of imAEs follow the guidelines outlined for ipilimumab (Weber, 2012). These guidelines recommend the following:

1. Subjects should be evaluated to identify any alternative etiology
2. In the absence of clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related
3. Symptomatic and topical therapy should be considered for low-grade events
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event
5. More potent immunosuppressives should be considered for events not responding to systemic steroids (eg, infliximab, mycophenolate, etc).

If the investigator has any question in regards to an AE being an imAE, the investigator should immediately contact the sponsor's medical monitor.

Dose reductions of durvalumab are not permitted. Dose modifications (ie, dose interruption, dose hold, or infusion rate modification) of durvalumab may be required in the event of treatment-related toxicity. General guidelines regarding dose modification are provided in Section 7.2.10.1.

7.2.10.3. Dose Modification for Lenalidomide (Discontinued to the Enrollment of New Subjects)

The dose of lenalidomide may be reduced successively by one level from the starting dose. There will be no more than one dose level reduction from one cycle to the next unless otherwise permitted after consultation with the sponsor's medical monitor. No dose (re)escalation is permitted at any time unless as specified in Table 25 and Table 26.

In addition, if a subject continues to experience unacceptable toxicity at the lowest dose level allowed, lenalidomide will be discontinued permanently.

Table 25: Lenalidomide Dose Modification Levels for Subjects Initiating Treatment at 20 mg Based on Pretreatment Creatinine Clearance ≥ 60 mL/min

Dose[a]	Once Daily on Days 1-21, Every 28-day Cycle
Level 1a **(starting dose)**	20 mg
Level -1a	15 mg
Level -2a	10 mg
Level -3a[b]	5 mg

[a] Once a subject's dose has been reduced, no dose re-escalation will be permitted.
[b] Subjects who cannot tolerate dose level -3a are to be discontinued from the Treatment Period of the study if the subject is receiving lenalidomide treatment only.

Table 26: Lenalidomide Dose Modification Levels for Subjects Initiating Treatment at 10 mg Based on Pretreatment Creatinine Clearance ≥ 40 mL/min and < 60 mL/min (Dose Confirmation and Expansion Parts Only)

Dose[a,b]	**Once Daily on Days 1-21, Every 28-day Cycle**
Level 2b[c]	15 mg
Level 1b **(starting dose)**	10 mg
Level -1b	5 mg
Level -2b[d]	2.5 mg

[a] If the subject has not experienced any drug-related ≥ Grade 3 toxicity for at least 2 cycles, the dose may be increased to 15 mg once daily on Days 1 to 21 of each 28-day cycle at the discretion of the treating physician from cycle 3 and onwards.

[b] Once a subject's dose has been reduced, no dose re-escalation is permitted.

[c] Once the dose is escalated to 15 mg once daily for 21 days of every 28-day cycle, the dose may be reduced successively by 1 level, ie, to 10 mg.

[d] Subjects who cannot tolerate dose level -2b are to be discontinued from the Treatment period of the study if the subject is receiving on lenalidomide treatment only.

The new cycle of treatment may begin on the scheduled Day 1 of the next cycle if all of the following requalification criteria for lenalidomide are met:

- A 7-day rest period has elapsed following the last dose of lenalidomide
- The absolute neutrophil count (ANC) is ≥ 1000 cells/mm³ (1.0×10^9/L);
- The platelet count is ≥ 50,000 cells/mm³ (50×10^9/L);
- Study-drug-related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity;
- Any other study-drug-related AE not requiring discontinuation has resolved to ≤ Grade 2 severity.

If these requalification criteria are not met on Day 1 of a new cycle, the subject will be evaluated at least once every 7 days until the toxicity has resolved as described above. If a new cycle is delayed for more than 28 days, the sponsor's medical monitor must be notified. The treatment can be resumed according to the investigators' and the sponsor's medical monitor's clinical judgment.

The criteria above do not apply to laboratory abnormalities of subjects who are randomized with these laboratory abnormalities due to lymphoma infiltration of the bone marrow or documented liver involvement by lymphoma. In the absence of evidence of treatment-emergent toxicity, the new cycle of treatment may begin at the discretion of the investigator.

Doses that were missed, because of toxicity or any other reason, will not be rescheduled.

7.2.10.4. Dose Modification for Rituximab

The dose of rituximab should not be reduced. The dose of rituximab may be interrupted and modified according to the clinical practice of the investigator's institution (eg, dose splitting or

dose banding), and in line with the approved prescribing information including administration, warnings, precautions, contraindications, and adverse reactions, as applicable.

In case a dose of rituximab (in Arm A or C) is missed during the first cycle because of toxicity, it will not be rescheduled. In such situations, treatment with other combination drugs does not need to be interrupted.

In case of delay in the start of next cycle during (eg, Cycles 2 to 5 in Arm A and Cycles 2 through 6 in Arm C) due to toxicity, rituximab administration may be postponed until AE has resolved, at which point the next cycle is started.

If rituximab is discontinued due to toxicity, the subject may continue receiving the other agents per the specified schedule.

7.2.10.5. Dose Modification for Ibrutinib

The dose of ibrutinib may be reduced successively by one level from the starting dose. There will be no more than one dose level reduction from one cycle to the next unless otherwise permitted after consultation with the sponsor's medical monitor. At the investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

In addition, if a subject continues to experience unacceptable toxicity at the lowest dose level allowed, ibrutinib will be discontinued permanently. If ibrutinib is discontinued due to toxicity, the subject may continue receiving durvalumab for up to 13 cycles. If durvalumab is discontinued due to toxicity, the subject will be discontinued from all study treatment.

Subjects who continue to receive ibrutinib on-study will be treated per investigator's medical judgement.

The dose reduction steps for ibrutinib are provided in Table 27 and Table 28:

Table 27: Ibrutinib Dose Modification Levels - NHL

Dose	**Once Daily Continuous**
Level 1a **(starting dose for NHL)**	560 mg
Level -1a	420 mg
Level -2a[a]	280 mg

Abbreviations: NHL = non-Hodgkin lymphoma.
[a] Subjects who cannot tolerate Dose Level -2a are to be discontinued from the Treatment Period of the study if the subject is receiving ibrutinib treatment only.

Table 28: Ibrutinib Dose Modification Levels - CLL

Dose	**Once Daily Continuous**
Level 1b **(starting dose for CLL)**	420 mg
Level -1b	280 mg
Level -2b[a]	140 mg

Abbreviations: CLL = chronic lymphocytic leukemia.

[a] Subjects who cannot tolerate Dose Level -2b are to be discontinued from the Treatment Period of the study if the subject is on ibrutinib treatment only.

7.2.10.6. Dose Modification for Bendamustine

The dose of bendamustine may be reduced successively by one level from the starting dose. At the investigator's discretion, the dose of bendamustine may be cautiously re-escalated in subsequent cycles in subjects with CLL.

In addition, if a subject continues to experience unacceptable toxicity at the lowest dose level allowed, bendamustine will be discontinued permanently. If bendamustine is discontinued due to toxicity, the subject may continue receiving durvalumab and/or rituximab for up to 13 cycles. If durvalumab is discontinued due to toxicity, the subject will be discontinued from all study treatment.

The dose reduction steps for bendamustine are provided in Table 29**:**

Table 29: Bendamustine Dose Modification Levels

Dose	**Days 1 and 2 of Cycles 1 through 4 or 6**
Level 1 **(starting dose for NHL)**	90 mg/m^2
Level -1 **(starting dose for CLL)**	70 mg/m^2
Level -2	50 mg/m^2

7.2.10.7. Dose Modification and Toxicity Management Guidelines

Dose modifications will not be required for AEs that are clearly not attributed to IPs or for laboratory abnormalities that are not deemed to be clinically significant (unless otherwise specified in Table 30, Table 31, and Table 32. If an AE occurs, the investigator should assess whether the AE is related to any of the IPs. If the AE is attributable to any IP based on the investigator's clinical judgment, then the investigator will follow the dose modification guidelines for that causative IP(s) provided in Table 30, Table 31, and Table 32.

Arm A (durvalumab plus lenalidomide with or without rituximab) is discontinued to the enrollment of new subjects. 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.

It is important to note that these guidelines prepared by the sponsor are to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities and should be applied to management of adverse events related to study treatment and not ANY adverse event.

In Arm B, subjects who continue to receive ibrutinib on-study will be treated per investigator's medical judgement.

Table 30: General Dose Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Immune-Mediated Reactions			Agent to be considered for dose modification
	Dose Modifications	**Toxicity Management**	
Immune-Mediated Adverse Events (imAEs) (Overall management of toxicities not described below)	Drug administration modifications of IP/study regimen will be made to manage potential immune-mediated AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of IP/regimen based on CTC AE grade/severity (table below), permanently discontinue IP/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of IP/regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing	It is recommended that management of immune-mediated adverse events (imAEs) follow the guidelines presented below: – It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (lasting more than 3 to 5 days) low-grade (Grade 2) or severe (≥ Grade 3) events promptly start prednisone PO 1-2 mg/kg/day PO or IV equivalent	durvalumab lenalidomide
	Grade 1: No dose modification Grade 2: Hold IP/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens, then treat as Grade 3 or Grade 4 • IP/study regimen can be resumed once event stabilizes to ≤ Grade 1 after completion of steroid taper		

Table 30: General Dose Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events (Continued)

Immune-Mediated Reactions			Agents to be considered for dose modification
	Dose Modifications	**Toxicity Management**	
Immune-Mediated Adverse Events (imAEs) (continued)	Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with IP/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The subject is clinically stable as per the investigator's or treating physician's clinical judgement. 3. Doses of prednisone are at ≤ 10 mg/day or equivalent.	– Some events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study doctor, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2-4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper).	durvalumab lenalidomide
	Grade 3: Depending on the individual toxicity, may permanently discontinue IP/study regimen. Please refer to guidelines below. Grade 4: Permanently discontinue IP/study regimen Note: For Grade 3 asymptomatic amylase or lipase levels, hold IP/study regimen and if complete work up shows no evidence of pancreatitis, may continue or resume IP/study regimen.		

Table 30: General Dose Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events (Continued)

Immune-Mediated Reactions			Agents to be considered for dose modification
	Dose Modifications	**Toxicity Management**	
Immune-Mediated Adverse Events (imAEs) (continued)	Note: IP/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether IP/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade < 1 upon treatment with systemic steroids and following full taper. Note: There are some exceptions to permanent discontinuation of IP/study regimen for Grade 4 events (ie., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	– More potent immunosuppressives such as TNF inhibitors (eg, infliximab) - (also refer to individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jiroveci pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of IP is not mandated for Grade 3 or Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc). Continuation of IP in this situation should be based upon a benefit-risk analysis for that subject.	durvalumab lenalidomide

Abbreviations: AE = adverse event; CTCAE = Common Toxicity Criteria for Adverse Events; imAE = immune-mediated adverse event; IP = investigational product; IV = intravenous; NCI = National Cancer Institute; PO = orally; TNF = tumor necrosis factor.

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Pneumonitis/ Interstitial Lung Disease (ILD)	Any Grade Grade of Pneumonitis (CTCAE version 4.03)	General Guidance	– Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan	durvalumab lenalidomide
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding IP/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) – Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated – Consider Pulmonary and Infectious disease consult	
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold IP/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1, then the decision to reinitiate IP/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper	For Grade 2 (Mild to Moderate New Symptoms) – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (eg, prednisone 1-2 mg/kg/day PO or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started – If still no improvement within 3-5 days despite IV methylprednisolone at 2-4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks).	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Pneumonitis/ Interstitial Lung Disease (ILD) (continued)			Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal or anti-Pneumocystis jiroveci pneumonia (PJP) treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation][a] – Consider pulmonary and infectious disease consult – Consider as necessary discussing with the sponsor's medical monitor	durvalumab lenalidomide
	Grade 3 or 4 Grade 3 (Severe symptoms; limiting self-care ADL; oxygen indicated) Grade 4 (Life-threatening respiratory compromise, urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue IP/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening) – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician – Hospitalize the subject – Supportive care (eg, oxygen) – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as tumor necrosis factor inhibitors (eg, infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Pneumonitis/ Interstitial Lung Disease (ILD) (continued)			– Once the subject is improving, gradually taper steroids over and consider prophylactic antibiotics, antifungal and in particular, anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) [a]	durvalumab lenalidomide
Diarrhea/ Colitis	Any Grade Grade of diarrhea (CTCAE version 4.03)	General Guidance	– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, infections including testing for clostridium difficile toxin) – Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event – Use analgesics carefully; they can mask symptoms of perforation and peritonitis	
	Grade 1 diarrhea (Stool frequency of < 4 over baseline per day) Grade 1 colitis (Asymptomatic; clinical or diagnostic observations only)	No dose modification	For Grade 1 diarrhea: – Close monitoring for worsening symptoms – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Diarrhea/ Colitis (continued)	Grade 2 diarrhea (Stool frequency of 4-6 over baseline per day) Grade 2 colitis (Abdominal pain; mucus or blood in stool)	Hold IP/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1, then IP/regimen can be resumed after completion of steroid taper	For Grade 2 diarrhea: – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – If still no improvement within 3-5 days despite 2-4 mg/kg IV methylprednisolone, promptly start immunosuppressives (infliximab at 5 mg/kg once every 2 weeks[a]). **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consider, as necessary, discussing with sponsor's medical monitor if no resolution to ≤ Grade 1 in 3-4 days – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) [a]	durvalumab lenalidomide

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Diarrhea/ Colitis (continued)	Grade 3 diarrhea (Stool frequency of ≥ 7 over baseline per day) Grade 3 colitis (Severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs)	Permanently discontinue IP/study regimen if toxicity does not improve to Grade ≤ 1 within 14 days; IP/study regimen can be resumed after completion of steroid taper.	For Grade 3 or 4 diarrhea: – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent – Monitor stool frequency and volume and maintain hydration – Urgent GI consult and imaging and/or colonoscopy as appropriate – If still no improvement within 3-5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg, infliximab at 5 mg/kg once every 2 weeks) – **Caution:** Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal, and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) [a]	durvalumab lenalidomide
	Grade 4 diarrhea (Life-threatening consequences) Grade 4 colitis (Life-threatening consequences, urgent intervention indicated)	Permanently discontinue IP/study regimen		

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune-mediated Hepatitis** **PLEASE SEE section below to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma patients**	Any Grade Grade of Liver Function Test Elevation (CTCAE version 4.03)		– Monitor and evaluate liver function test (LFT): AST, ALT, ALP and total bilirubin (TB) – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications)	durvalumab lenalidomide
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and <1.5 × ULN)	No dose modification If it worsens, treat as Grade 2 event	For Grade 1 AST or ALT and/or TB elevation: – Continue LFT monitoring per protocol	
	Grade 2 (AST or ALT >3.0 ×ULN and ≤5.0×ULN and/or TB >1.5×ULN and <3.0 × ULN)	Hold IP/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens, then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline, resume IP/study regimen after completion of steroid taper	For Grade 2 AST or ALT and/or TB elevation: – Regular and frequent checking of LFTs (eg, every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, consider, as necessary, discussing with the sponsor's medical monitor. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day PO or IV equivalent. – If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started – If still no improvement within 3-5 days despite 2-4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (ie, mycophenolate mofetil). [a] Discuss with the sponsor's medical monitor if mycophenolate mofetil is not available. **Infliximab should NOT be used.**	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Hepatitis (Elevated LFTs) (continued)			– Once the subject is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) [a]	durvalumab lenalidomide
Infliximab should not be used for management of Immune-mediated Hepatitis **PLEASE SEE section below to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma patients**	Grade 3 (AST or ALT >5.0 ×ULN and ≤20.0×ULN and/or TB >3.0×ULN and <10.0 × ULN)	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN • Hold IP/study regimen dose until resolution to ≤ Grade 1 or baseline • Resume IP/study regimen if elevations downgrade ≤ Grade 1 or baseline within 14 days, and after completion of steroid taper • Permanently discontinue IP/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days	For Grade 3 or 4 AST or ALT and/or TB elevation: – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent – If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (ie, mycophenolate mofetil). Discuss with the sponsor's medical monitor if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the subject is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) [a]	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Hepatitis (Elevated LFTs) (continued) **Infliximab should not be used for management of Immune-mediated Hepatitis**		For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue IP/study regimen Permanently discontinue IP/study regimen for any case meeting Hy's law criteria (AST and/or ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (ie, elevated alkaline phosphatase) and in the absence of any alternative cause[b]		durvalumab lenalidomide
PLEASE SEE section below to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma patients	Grade 4 (AST or ALT >20 ×ULN and/or TB >10×ULN)	Permanently discontinue IP/study regimen		

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune-mediated Hepatitis** **This section is *only* for management of "Hepatitis (elevated LFTs)" in hepatocellular carcinoma patients** See instructions at bottom of table if transaminase rise is not isolated but (at any time) occurs in setting of either i**ncreasing bilirubin or signs of DILI/liver decompensation**	Any Grade	For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	– Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [eg, portal vein thrombosis]). – For HBV+ subjects: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ subjects: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any subject with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above	durvalumab lenalidomide
	Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event		

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Hepatitis (Elevated LFTs) (continued) **Infliximab should not be used for management of Immune-mediated Hepatitis** **This section is *only* for management of "Hepatitis (elevated LFTs)" in hepatocellular carcinoma patients** See instructions at bottom of table if transaminase rise is not isolated but (at any time) occurs in setting of either i**ncreasing bilirubin or signs of DILI/liver decompensation**	Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold IP/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume IP/study regimen after completion of steroid taper.	For Grade 2: – Regular and frequent checking of LFTs (eg, every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (ie, liver ultrasound), and consider starting immunosuppressives (ie, mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**	durvalumab lenalidomide

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Hepatitis (Elevated LFTs) (continued) **Infliximab should not be used for management of Immune-mediated Hepatitis** **This section is *only* for management of "Hepatitis (elevated LFTs)" in hepatocellular carcinoma patients** See instructions at bottom table if transaminase rise is not isolated but (at any time) occurs in setting of either i**ncreasing bilirubin or signs of DILI/liver decompensation**	Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	• Hold IP/study regimen dose until resolution to Grade ≤1 or baseline • Resume IP/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue IP/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days • Permanently discontinue IP/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	For Grade 3: − Regular and frequent checking of LFTs (eg, every 1-2 days) until elevations of these are improving or resolved. − Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. − Consider, as necessary, discussing with study physician. − If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. − If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** − Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]	durvalumab lenalidomide

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Hepatitis (Elevated LFTs) (continued) **Infliximab should not be used for management of Immune-mediated Hepatitis** **This section is *only* for management of "Hepatitis (elevated LFTs)" in hepatocellular carcinoma patients**	Grade 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue IP/study regimen.	For Grade 4: Same as above (except would recommend obtaining liver biopsy early)	durvalumab lenalidomide
See instructions at bottom of table if transaminase rise is not isolated but (at any time) occurs in setting of either i**ncreasing bilirubin or signs of DILI/liver decompensation**	**If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (eg, fever, elevated INR):** - **Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise** - **Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise** - **Grade 3-4: Permanently discontinue IP/study regimen**			

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Any Grade Grade of Elevated Serum Creatinine (CTCAE version 4.03)	General Guidance	– Consult with nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria) – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections) teroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) in order to prevent potential progression to higher grade event	durvalumab lenalidomide
	Grade 1 (Serum Creatinine > 1-1.5 × baseline; > ULN to 1.5 × ULN)	No dose modification	For Grade 1 elevated creatinine: – Monitor serum creatinine weekly and any accompanying symptoms • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity, treat as Grade 2, 3 or 4 – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics	
	Grade 2 (Serum Creatinine >1.5-3.0 × baseline; >1.5-3.0 × ULN)	Hold IP/study regimen until resolution to ≤Grade 1 or baseline • If toxicity worsens, then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline, then resume IP/study regimen after completion of steroid taper	For Grade 2 elevated creatinine: – Consider symptomatic treatment including hydration, electrolyte replacement, and diuretics – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult nephrologists and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Nephritis or Renal Dysfunction (Elevated Serum Creatinine) (continued)			– If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. – Once the subject is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) [a] – When event returns to baseline, resume IP/study regimen and routine serum creatinine monitoring per study protocol.	durvalumab lenalidomide
	Grade 3 (Serum Creatinine > 3.0 × baseline; > 3.0-6.0 × ULN) Grade 4 (Serum Creatinine > 6.0 × ULN)	Permanently discontinue IP/study regimen	For Grade 3 or 4 elevated creatinine: – Carefully monitor serum creatinine on daily basis – Consult nephrologist and consider renal biopsy if clinically indicated – Promptly start prednisone 1-2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – Once the subject is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) [a]	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Rash (excluding Bullous skin formations)	Any Grade (refer to NCI CTCAE version 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	– Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE SPONSOR'S MEDICAL MONITOR SHOULD BE CONTACTED **AND IP/REGIMEN DISCONTINUED****	durvalumab lenalidomide
	Grade 1	No dose modification	For Grade 1: – Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream)	
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled IP/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens, then treat as Grade 3 • If toxicity improves ≤ Grade 1 or baseline, then resume IP/study regimen after completion of steroid taper	For Grade 2: – Obtain dermatology consult – Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with the sponsor's medical monitor and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent – Consider skin biopsy if persistent for > 1-2 weeks or recurs	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Rash (excluding Bullous skin formations) (continued)	Grade 3	Hold IP/study regimen until resolution to ≤ Grade 1 or baseline • If temporarily holding the IP/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue IP/study regimen	For Grade 3 or 4: – Consult dermatology – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Consider, as necessary, discussing with the sponsor's medical monitor	durvalumab lenalidomide
	Grade 4	Permanently discontinue IP/study regimen		

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, adrenal insufficiency); exocrine event of amylase/lipase increased also included in this section	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)	General Guidance	– Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension and weakness. – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, infections) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, fT3 and fT4 and other relevant endocrine and related labs (eg, blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a subject experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing	durvalumab lenalidomide
	Grade 1	No dose modification	For Grade 1 (including those with asymptomatic TSH elevation): – Monitor subject with appropriate endocrine function tests – For suspected hypophysitis/hypopituitarism, consider	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, adrenal insufficiency); exocrine event of amylase/lipase increased also included in this section (continued)			consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH > 2 × ULN, or consistently out of range in 2 subsequent measurements, include fT4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.	durvalumab lenalidomide
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold IP/study regimen dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 • IP/study regimen can be resumed once event stabilizes to ≤ Grade 1 and after completion of steroid taper.	For Grade 2: (including those with symptomatic endocrinopathy) – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all subjects with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term, corticosteroids (eg, 1-2 mg/kg/day methylprednisone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without IP/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without IP/study regimen interruption, and without corticosteroids.	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, adrenal insufficiency); exocrine event of amylase/lipase increased also included in this section (continued)		Subjects with endocrinopathies who may require prolonged or continued steroid replacement (eg, adrenal insufficiency) can be retreated with IP/study regimen on the following conditions: 1.The event stabilizes and is controlled. 2. The subject is clinically stable as per the investigator's or treating physician's clinical judgement. 3. Doses of prednisone are at ≤ 10 mg/day or equivalent.	– Once subjects on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – For subjects with normal endocrine work up (laboratory or MRI scans), repeat labs/MRI as clinically indicated.	durvalumab lenalidomide
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus: • Hold IP/study regimen dose until endocrinopathy symptom(s) are controlled • IP/study regimen can be resumed once event stabilizes and after completion of steroid taper.	For Grade 3 or 4: – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all subjects with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (eg, hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity.	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, adrenal insufficiency); exocrine event of amylase/lipase increased also included in this section (continued)		Patients with endocrinopathies who may require prolonged or continued steroid replacement (eg, adrenal insufficiency) can be retreated with IP/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– Isolated hypothyroidism may be treated with replacement therapy, without IP/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without IP/study regimen interruption, and without corticosteroids.Once subjects on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) [a]	durvalumab lenalidomide
Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis and autonomic neuropathy, **excluding Myastenia Gravis and Guillain-Barre)**	Any Grade (Depending on the type of neurotoxicity, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)	General Guidance	– Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications) – Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations) – Perform symptomatic treatment with neurological consult as appropriate	
	Grade 1	No dose modifications	– See "Any Grade" recommendations above.	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis and autonomic neuropathy, **excluding Myastenia Gravis and Guillain-Barre)** (continued)	Grade 2	• For acute motor neuropathies or neurotoxicity, hold IP/study regimen dose until resolution to ≤ Grade 1 • For sensory neuropathy/neuropathic pain, consider holding IP/study regimen dose until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • IP/study regimen can be resumed once event improves to ≤ Grade 1 and after completion of steroid taper.	– Consider, as necessary, disccusing with the sponsor's medical monitor – Obtain Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc) – Promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent – If no improvement within 3-5 days despite 1-2 mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IV IG)	durvalumab lenalidomide
	Grade 3	• Hold IP/study regimen dose until resolution to ≤ Grade 1 • Permanently discontinue IP/study regimen if Grade 3 imAE does not resolve to ≤ Grade 1 within 30 days.	For Grade 3 or 4: – Consider, as necessary, discussing with the sponsor's medical monitor – Obtain neurology consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IV IG) – Once stable, gradually taper steroids over ≥ 28 days	
	Grade 4	• Permanently discontinue IP/study regimen		

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Immune-mediated peripheral neuromotor syndromes, **such as Guillain-Barre and Myasthenia Gravis**	Any Grade	General Guidance	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG	durvalumab lenalidomide

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Immune-mediated peripheral neuromotor syndromes, **such as Guillain-Barre and Myasthenia Gravis** (continued)	Grade 1	No dose modification	– Consider, as necessary, disccusing with the sponsor's medical monitor – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above – Obtain a neurology consult.	durvalumab lenalidomide
	Grade 2	• Hold IP/study regimen dose until resolution to ≤ Grade 1 • Permanently discontinue IP/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For Grade 2: – Consider, as necessary, discussing with the sponsor's medical monitor – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist.	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Immune-mediated peripheral neuromotor syndromes, **such as Guillain-Barre and Myasthenia Gravis** (continued)			○ Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each subject ○ If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.	durvalumab lenalidomide

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Immune-mediated peripheral neuromotor syndromes, **such as Guillain-Barre and Myasthenia Gravis** (continued)	Grade 3	• Hold IP/study regimen dose until resolution to ≤ Grade 1Permanently discontinue IP/study regimen if Grade 3 imAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For Grade 3 or 4 (severe or life threatening (Grade 3 or 4) events): – Consider, as necessary, discussing with the sponsor's medical monitor – Recommend hospitalization – Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IV IG.	durvalumab lenalidomide
	Grade 4	• Permanently discontinue IP/study regimen		

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Myocarditis	Any Grade	General Guidance • Discontinue drug permanently if biopsy-proven immune-mediated myocarditis	For Any Grade: − The prompt diagnosis of immune-mediated myocarditis is important, particularly in subjects with baseline cardiopulmonary disease and reduced cardiac function. − Consider, as necessary, discussing with the study physician. − Monitor subjects for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (eg, pulmonary embolism, congestive heart failure, malignant pericardial effusion). A cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. − Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. − Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections)	durvalumab lenalidomide
	Grade 1 (asymptomatic with laboratory (eg, BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold IP/study regimen dose during diagnostic work-up for other etiologies. If IP/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** − Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. − Consider using steroids if clinical suspicion is high.	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Myocarditis (continued)	**Grade 2, 3 or 4** Grade 2 (Symptoms with mild to moderate activity or exertion) Grade 3 (Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) Grade 4 (Life-threatening consequences; urgent intervention indicated (eg, continuous IV therapy or mechanical hemodynamic support))	• If Grade 2, hold IP/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate IP/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue IP/study regimen. • If Grade 3-4, permanently discontinue IP/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]	durvalumab lenalidomide

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Myositis/Polymyositis ("Poly/myositis")	Any Grade	• General Guidance	For Any Grade: – Monitor subjects for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (ie, consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider barium swallow	durvalumab lenalidomide

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Myositis/Polymyositis ("Poly/myositis") (continued)			for evaluation of dysphagia or dysphonia. – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections).	durvalumab lenalidomide
	Grade 1 (mild pain)	No dose modifications	For Grade 1: – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider neurology consult. – Consider, as necessary, discussing with the study physician.	
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	• Hold IP/study regimen dose until resolution to Grade ≤1. • Permanently discontinue IP/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	For Grade 2: – Monitor symptoms daily and consider hospitalization. – Obtain neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors	

Table 31: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Myositis/Polymyositis ("Poly/myositis") (continued)			– (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]	durvalumab lenalidomide
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	For Grade 3: • Hold IP/study regimen dose until resolution to Grade ≤1. • Permanently discontinue IP/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. For Grade 4: Permanently discontinue IP/study regimen.	For Grade 3 or 4 (severe or life-threatening events): – Monitor symptoms closely; recommend hospitalization. – Obtain neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether subject may require IV IG plasmapheresis. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]	

Abbreviations: AChE = acetylcholine esterase; ACTH = adrenocorticotropic hormone; ADL = activities of daily living; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CT = computed

tomography; CTC = common terminology criteria; CTCAE = common terminology criteria for adverse events; DILI = drug incuded liver injury; ECG = electrocardiogram; fT3 = free triiodothronine; fT4 = free thyroxine; GI = gastrointestinal; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IgG = Immunoglobulin; ILD = interstitial lung disease; IM = intramuscular; IP = investigational product; imAE = immune-mediated adverse event; IV = intravenous; IVIG = intravenous immune globulin; LDH = lactic dehydrogenase; LFT = liver function test; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; NCI = National Cancer Institute; PJP = *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO = orally; TB = total bilirubin; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" (Postow, 2015).
[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury - Premarketing Clinical Evaluation NCI CTCAE version 4.03.

Table 32: Dose Modification and Toxicity Management Guidelines for NON Immune-mediated Reactions

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to IP/regimen (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant. **The following guidelines are not inclusive of all toxicities identified for each treatment. Please refer to the locally approved label of each treatment for additional guidelines as needed.**			
Neutropenia * unless secondary to lymphomatous/CLL bone marrow involvement	Grade 3 (ANC < 1000 cells/mm³ [1x10^9/L])	**durvalumab:** • Hold IP/study regimen until resolution to ≤ Grade 1 or baseline • For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume IP/study regimen administration. Otherwise, discontinue IP/study regimen **rituximab:** • Follow your institutional standard or locally approved rituximab label as applicable **lenalidomide:** • If sustained (≥ 7 days) Grade 3 or Grade 3 associated with fever (temperature ≥ 38.5°C), hold lenalidomide dose • If neutropenia resolves to ≤ Grade 2 (ANC ≥1000 /mm^3[≥1 × 10^9/L]), restart lenalidomide at next lower dose level **ibrutinib:** • Hold ibrutinib if Grade 3 associated with infection or fever (temperature ≥ 38.5°C) • If neutropenia resolves to ≤ Grade 1 (ANC ≥1500 /mm3 [≥1.5 × 10^9/L]) or baseline, restart the dose. If toxicity recurs, reduce dose by 140 mg. If toxicity	• Monitor CBC with differential at least weekly • Use of growth factors (G-CSF, GM-CSF) is permitted as per ASCO or ESMO Guidelines	bendamustine lenalidomide ibrutinib rituximab durvalumab

Table 32: Dose Modification and Toxicity Management Guidelines for NON Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Neutropenia * unless secondary to lymphomatous/CLL bone marrow involvement (continued)		persists following 2 dose reductions, discontinue ibrutinib **bendamustine:** • Delay bendamustine until neutropenia resolves to Grade 2 (ANC≥1000 /mm^3[≥1 × 10^9/L]) **In CLL only:** • Reduce bendamustine dose to next lower dose level on Days 1 and 2 of subsequent cycles • May cautiously re-escalate bendamustine dose in subsequent cycles at the investigator's discretion		bendamustine lenalidomide ibrutinib rituximab durvalumab
	Grade 4 (ANC < 500 cells/mm³ [0.5x10^9/L])	**durvalumab:** • Decision to discontinue would be based on accompanying clinical signs/symptoms and as per investigator's clinical judgment and in consultation with the sponsor **rituximab:** • Follow your institutional standard or locally approved rituximab label as applicable **lenalidomide:** • Hold lenalidomide dose • If neutropenia resolves to ≤ Grade 2 (ANC ≥1000 /mm^3[≥1 × 10^9/L]), restart lenalidomide at next lower dose level **ibrutinib:** • Hold ibrutinib if Grade 4 associated with infection or fever (temperature ≥ 38.5°C)	• Monitor CBC with differential at least weekly • Use of growth factors (G-CSF, GM-CSF) is permitted as per ASCO or ESMO Guidelines	

Table 32: Dose Modification and Toxicity Management Guidelines for NON Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Neutropenia * unless secondary to lymphomatous/CLL bone marrow involvement (continued)		• If neutropenia resolves to ≤ Grade 1 (ANC ≥1500 /mm^3 [≥1.5 × 10^9/L]) or baseline, restart the dose. If toxicity recurs, reduce dose by 140 mg. If toxicity persists following 2 dose reductions, discontinue ibrutinib **bendamustine:** • Delay bendamustine until neutropenia resolves to Grade 2 (ANC ≥1000 /mm^3 [≥1 × 10^9/L]) • Reduce bendamustine dose to next lower dose level on Days 1 and 2 of subsequent cycles • **In CLL only:** May cautiously re-escalate bendamustine dose in subsequent cycles at the investigator's discretion		bendamustine lenalidomide ibrutinib rituximab durvalumab
Thrombocytopenia * unless secondary to lymphomatous/CLL bone marrow involvement	Grade 3 (Platelets <50,000 cells /mm^3 [50 × 0^9/L])	**durvalumab:** • Hold IP/study regimen until resolution to ≤ Grade 1 or baseline • For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume IP/study regimen administration. Otherwise, discontinue IP/study regimen **rituximab:** • Follow your institutional standard or locally approved rituximab label as applicable	• Monitor CBC with differential at least weekly • Platelet transfusion is permitted as per ASCO Guidelines	bendamustine lenalidomide ibrutinib rituximab durvalumab

Table 32: Dose Modification and Toxicity Management Guidelines for NON Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Thrombocytopenia * unless secondary to lymphomatous/CLL bone marrow involvement (continued)		**lenalidomide:** • Hold lenalidomide dose • If thrombocytopenia resolves to ≤ Grade 2 (platelets ≥50,000 cells /mm³ [50 ×10^9/L], restart lenalidomide at next lower dose **ibrutinib:** • No dose modification required **bendamustine:** • Delay treatment until thrombocytopenia resolve to Grade 1 ≥75,000/mm^3[≥75 × 10^9/L]) • Reduce dose to next lower dose level on Days 1 and 2 of subsequent cycles **In CLL only:** May cautiously re-escalate dose in subsequent cycles at the investigator's discretion		bendamustine lenalidomide ibrutinib rituximab durvalumab
	Grade 4 (Platelets <25,000 cells /mm³ [25 × 10^9/L])	**durvalumab:** • Decision to discontinue would be based on accompanying clinical signs/symptoms and as per investigator's clinical judgment and in consultation with the sponsor **rituximab:** • Follow your institutional standard or locally approved rituximab label as applicable	• Monitor CBC with differential at least weekly Platelet transfusion is permitted as per ASCO Guidelines	

Table 32: Dose Modification and Toxicity Management Guidelines for NON Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Thrombocytopenia * unless secondary to lymphomatous/CLL bone marrow involvement (continued)		**lenalidomide:** • Hold lenalidomide • If thrombocytopenia resolves to ≤ Grade 2 (platelets ≥50,000 cells /mm³ [50 × 10^9/L], restart lenalidomide at next lower dose **ibrutinib:** • Hold ibrutinib • If thrombocytopenia resolves to ≤ Grade 1 (platelets ≥75,000 cells /mm³ [75 × 109/L] or baseline, restart the dose. If toxicity recurs, reduce dose by 140 mg. If toxicity persists following 2 dose reductions, discontinue ibrutinib **bendamustine:** • Delay treatment until thrombocytopenia resolves Grade 1 ≥75,000/mm^3[≥75 × 10^9/L]) **In CLL only:** • Reduce dose to next lower dose level on Days 1 and 2 of subsequent cycles • May cautiously re-escalate dose in subsequent cycles		bendamustine lenalidomide ibrutinib rituximab durvalumab
Stevens-Johnson Syndrome or toxic epidermal necrosis	--	**Discontinue all the agents**	--	bendamustine lenalidomide ibrutinib rituximab durvalumab

Table 32: Dose Modification and Toxicity Management Guidelines for NON Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Thrombo-embolic event (Venous thrombosis/ Embolism)	Grade 3 or 4	**rituximab:** • Follow your institutional standard or locally approved rituximab label as applicable **lenalidomide:** • Hold lenalidomide and start anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level) **ibrutinib:** • Discontinue ibrutinib **bendamustine:** • Delay bendamustine; start anticoagulation; restart at investigator's discretion	• Start anticoagulation treatment	lenalidomide rituximab bendamustine ibrutinib
Hypothyroidism (if not immune-mediated)	If the TSH is > ULN and subject is clinically euthyroid If TSH is > ULN for more than 2 cycles, or if subject has clinical symptoms of hypothyroidism	**lenalidomide:** • No dose reduction or interruption • For other IPs, please see other non-hematologic AEs below **lenalidomide:** • No dose reduction or interruption Note: For other IPs, please see other non-hematologic AEs below	• Repeat TSH on Day 1 of next cycle • Endocrinology evaluation is recommended and thyroid hormone replacement is allowed if clinically indicated	lenalidomide

Table 32: Dose Modification and Toxicity Management Guidelines for NON Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Hyperthyroidism (if not immune-mediated)	If TSH < LLN and subject is clinically euthyroid	**lenalidomide:** • No dose reduction or interruption Note: For other IPs, please see other non-hematologic AEs below	• Repeat TSH at least every 3 months	lenalidomide
	If TSH <LLN at repeat evaluation and subject is clinically euthyroid	**lenalidomide:** • No dose reduction or interruption Note: For other IPs, please see other non-hematologic AEs below	• Recommend endocrine evaluation	
	If TSH < LLN and subjects have symptoms of hyperthyroid (tremor, tachycardia, unintentional weight loss, or *new onset* night sweats)	**lenalidomide:** • Hold lenalidomide • If endocrine evaluation rules out hyperthyroidism, restart lenalidomide at the same dose • If hyperthyroidism confirmed and alternative etiologies eliminated, restart lenalidomide at next lower dose Note: For other IPs, please see other non-hematologic AEs below	• Obtain endocrine evaluation and workup for alternative etiologies • Repeat TSH level on Day 1 of next cycle and contact the sponsor's medical monitor	

Table 32: Dose Modification and Toxicity Management Guidelines for NON Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Liver Function (if not immune-related)	ALT/ AST ≥ Grade 3 (> 5 × ULN) OR Total bilirubin ≥ Grade 2 (> 1.5 xULN)	**lenalidomide:** • Hold lenalidomide • Restart lenalidomide if resolves to baseline within ≤ 14 days • If the resolution to baseline prolongs beyond 14 days and restart lenalidomide at next lower dose • For other IPs, please see other non-hematologic AEs below	• Follow weekly ALT/AST and total bilirubin until returns to baseline • Repeat liver function test at least weekly to resolution	lenalidomide
Other AEs	Grade 2	**durvalumab (not-immune mediated):** • Hold durvalumab until resolution to ≤ Grade 1 or baseline **rituximab/lenalidomide/ibrutinib:** • No dose reduction or interruption **bendamustine:** • May continue bendamustine at the investigator's discretion	Treat accordingly as per local/institutional guidelines • Treat accordingly as per local/institutional guidelines	--- --

Table 32: Dose Modification and Toxicity Management Guidelines for NON Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Other AEs (continued)	Grade 3 or 4	**durvalumab:** • **Grade 3**: Hold durvalumab until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume IP/study regimen administration.. Otherwise, discontinue IP/study regimen • **Grade 4:** Discontinue IP/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per investigator's clinical judgment and in consultation with the sponsor) **rituximab:** • Follow your institutional standard or locally approved rituximab label as applicable **lenalidomide:** • Hold lenalidomide and restart at same when toxicity resolves to ≤ Grade 2 or next lower dose at the investigator's discretion	• Treat accordingly as per local/institutional guidelines	

Table 32: Dose Modification and Toxicity Management Guidelines for NON Immune-mediated Reactions (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Other AEs (continued)		**ibrutinib:** • Hold ibrutinib • If toxicity resolves to ≤ Grade 1 or baseline, restart the dose. If toxicity recurs, reduce dose by 140 mg. If toxicity persists following 2 dose reductions, discontinue ibrutinib **Bendamustine:** • Delay treatment until resolves to ≤Grade 1 • Reduce dose to next lower bendamustine dose. **In CLL:** May cautiously re-escalate dose in subsequent cycles		--

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; CBC = complete blood count; CLL = chronic lymphocytic leukemia; ESMO = European Society of Medical Oncology; GCSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IP = investigational product; LLN = lower limit of normal; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = non steroidal antiinflammatory drug; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

Table 33: Dose Modification and Toxicity Management Guidelines for Infusion-related Reactions

Toxicity	Severity Grade of the Event (NCI CTCAE version 4.03	Dose Modification	Toxicity Management
Infusion-related Reactions	Any Grade	General Guidance	• Management per institutional standard at the discretion of investigator • Monitor subjects for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, tachycardia)
Infusion-related Reactions	Grade 1	• The infusion rate of IP/regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: • Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator • Consider premedication per institutional standard prior to subsequent doses for durvalumab/bendamustine • Steroids should not be used for routine premedication of ≤ Grade 2 infusion reactions
Infusion-related Reactions	Grade 2	• The infusion rate of study drug/regimen may be decreased 50% or temporarily interrupted until resolution of the event • Subsequent infusions may be given at 50% of the initial infusion rate	
Infusion-related Reactions	Grade 3/4	• Permanently discontinue durvalumab/study regimen	For Grade 3 or 4: • Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

Abbreviations: IM = intramuscular; IP = investigational product; IV = intravenous; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events.

7.3. Method of Treatment Assignment

Assignment of subjects to Arms A, B, C, and D, or each planned disease cohort within a treatment arm will be based on current open dose levels (DL) and available slots.

Arm A is discontinued to the enrollment of new subjects. Only subjects currently enrolled and receiving clinical benefit, based on the discretion of the Investigator, can remain on treatment after being informed and reconsent.

An IRT will be used to track subject assignments to the treatment arms and dose levels.

7.4. Overdose

Overdose, as defined for this protocol, refers to durvalumab (IV), lenalidomide (PO), ibrutinib (PO), rituximab (IV), bendamustine (IV), or local IFRT (involved field radiation therapy). On a per-dose basis, an overdose is defined as the following amount over the protocol-specified dose of these drug(s) assigned to a given subject, regardless of any associated AEs or sequelae:

- PO: any amount over the protocol-specified dose
- IV: 10% over the protocol-specified dose
- Radiation therapy: any amount over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the CRF. See Section 10 for the reporting of AEs associated with overdose.

7.5. Packaging and Labeling

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.6. Investigational Product Accountability and Disposal

The investigator(s) or designee is responsible for taking an inventory of each shipment of investigational product received and comparing it with the accompanying shipping order/packaging slip. The investigator(s) will verify the accuracy of the information on the shipping order/packaging slip and call IRT to register receipt at the site of the investigational product.

At the study site, investigational product will be stored in a locked, safe area to prevent unauthorized access and should be stored as directed on the product label.

An accurate accounting of the dispensing and return of investigational product for each study subject will be maintained in source documents on an ongoing basis by a member of the study site staff. Additionally, if any investigational product is lost or damaged or if the study subject misses a dose, this information should be documented in the study subject's CRF and source documents.

Celgene will instruct the investigator on the return, disposal, and/or destruction of unused investigational product.

7.7. Investigational Product Compliance

For the oral medications of lenalidomide or ibrutinib, study personnel will review the dosing instructions with the subject prior to dispensing investigational product. The subject will be instructed to return the investigational product bottles or blister cards, including any unused investigational product, to the site at the end of the applicable treatment cycle. To monitor treatment compliance, the subject will be interviewed at each applicable visit regarding whether they took their medication, and a reconciliation of capsules/tablets will be done upon bottle or blister card return. Subject compliance will be noted in the source records and on the appropriate CRFs based upon the interview and tablet/capsule count.

For the IV medications of durvalumab, rituximab, and bendamustine or local IFRT, the planned and administered dosage will be recorded in the source records and on the appropriate CRFs.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression. Supportive care, including, but not limited to antiemetic medications, may be administered at the discretion of the investigator.

All concomitant treatments, including blood and blood products, used from 28 days prior to first dose of any IP until 90 days after the last dose of durvalumab or 28 days after the last dose of other IPs, whichever occurs later, must be reported on the CRF.

For information regarding other drugs that may interact with any IP and affect its metabolism, pharmacokinetics, or excretion, please see the IB and/or local package insert.

8.1. Permitted/Recommended Concomitant Medications and Procedures

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 8.2.

Specifically, subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

8.1.1. Growth Factors and Transfusions for Cytopenia (All Arms)

Growth factors (eg, G-CSF, GM-CSF, erythropoietin, etc) may be prescribed during the Treatment and Follow-up Periods at the investigator's discretion and should be used in accordance with the American Society of Clinical Oncology's (ASCO) guidelines or the European Society for Medical Oncology guidelines.

Granulocyte colony stimulating factor is recommended to be used to mitigate the duration of neutropenia for any subject requiring a dose modification due to neutropenia.

Growth factors or platelet transfusions should not be administered during the Screening Period to increase a subject's blood values in order to meet entry criteria.

In Phase 1, Dose Finding: Erythropoietic and hematopoietic growth factors (eg, filgrastim and pegfilgrastim) as well as transfusional support (packed red blood cells and platelets) should not be given during the DLT observation period. If they are administered this will be an indication of possible DLT. However, it is permitted at the investigator's discretion after a subject completes the first cycle or within the first cycle if a hematological DLT has already been declared for that subject.

8.1.2. Infection Prophylaxis (All Arms)

Investigators may use their discretion in administering infection prophylaxis for subjects regarded to be at high risk (including, for example, but not limited to: acyclovir or similar drug for herpes zoster; trimethoprim/sulfamethoxazole for Pneumocystis jiroveci infection). Monitor patients for fever, neutropenia and infections and appropriate antiinfective therapy should be instituted as indicated.

8.1.3. Venous Thromboembolism Prophylaxis (Lenalidomide)

It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide may lessen the potential for venous thromboembolism (VTE). The decision to take prophylactic measures should be made carefully after an assessment of an individual subject's underlying risk factors.

As reference information, for subjects receiving lenalidomide in open-label trials, it is strongly recommended that subjects at risk for VTE receive either aspirin (70 – 325 mg PO daily) or another prophylaxis agent while on lenalidomide. In those subjects with a high risk of VTE, it is strongly recommended that the subject receive prophylactic anticoagulation therapy with low molecular weight heparin, or heparin (dose recommended for the prophylaxis of deep vein thrombosis/ pulmonary embolism per the package insert), or warfarin (to maintain an INR of 2.0). The choice of VTE prophylaxis agent relies upon the investigator's discretion and should be tailored to the subject's individual risk/benefit profile by taking into account the individual thrombotic risk, bleeding risk, and the quality of compliance with the VTE prophylaxis.

8.1.4. Nausea Prophylaxis (Bendamustine)

Premedication with an antiemetic prior to bendamustine infusion is recommended according to local practice.

8.1.5. Infusion Reaction Prophylaxis (Rituximab, Bendamustine, Durvalumab)

Premedication consisting of acetaminophen and an antihistamine should be administered before each rituximab infusion (see package insert or where applicable refer to the instruction in the Pharmacy Manual). Steroids may also be administered before the start of the rituximab infusion according to institutional practice. Surveillance measures during and after infusion of rituximab should be applied as recommended by the manufacturer/current guidelines.

Infusion reactions with bendamustine, which may include chills, fever, pruritus, and rash, are common. Rarely, anaphylactic and anaphylactoid reactions have occurred, particularly with the second or subsequent cycle(s).

Subjects who experienced grade 3 or higher allergic reactions should not be re-challenged but premedication with antihistamines, antipyretics and corticosteroids for subjects with a history of Grade 1 or 2 infusion reactions should be considered for bendamustine or durvalumab.

8.1.6. Early Antitumor Response (eg, Pseudoprogression, Flare Reaction) Treatment (All Arms)

Early antitumor response (eg, pseudoprogression, flare reaction) is defined as a sudden and tender increase in the size of the disease bearing sites, including the lymph nodes, spleen and/or the liver often accompanied by low-grade fever, diffuse rash and in some cases increase in the peripheral blood lymphocyte counts. Its treatment is up to the discretion of the investigator depending upon the severity and clinical situation. It is suggested that Grades 1 and 2 events be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) (ie, ibuprofen 400 to 600 mg orally every 4 to 6 hours as needed), corticosteroids, and/or narcotic analgesics for pain management. In mild to moderate (Grades 1 and 2) cases, it is suggested that IP be continued along with symptomatic treatment as above.

In more severe cases, IP should be interrupted, as indicated, and treatment with corticosteroids, NSAIDs, narcotic analgesics, and or antihistamines is suggested. Refer to Section 7.2.10.7 for further instructions and dose modifications for Grades 3 and 4 events.

During the Treatment Period, emergency use of corticosteroids at any dose to treat the symptoms of this event is allowed at the investigator's discretion.

8.1.7. Tumor Lysis Syndrome Prophylaxis or Treatment (All Arms)

It is recommended that subjects receive tumor lysis syndrome (TLS) prophylaxis or treatment (allopurinol or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of treatment administration in the first cycle, or as clinically indicated. Hydration levels should be adjusted according to age and clinical status. To monitor for TLS, the subjects will have close monitoring of blood chemistry during the first few cycles and additionally as clinically indicated.

Tumor lysis syndrome will be assessed by the Cairo-Bishop Grading system (Appendix D) (not by NCI CTCAE) and the assessment includes both laboratory tumor lysis syndrome (LTLS) criteria and clinical TLS criteria. If a subject develops LTLS (defined by the presence of 2 or more serum value abnormalities of uric acid, potassium, phosphorous, or calcium) or ≥ Grade 1 TLS (defined by the presence of laboratory TLS and one or more of the following criteria: creatinine ≥ 1.5 × ULN, arrhythmia, or seizures), appropriate medical management should be initiated according to the local standard of care in each institution, along with vigorous IV hydration.

Rasburicase for treatment of TLS is considered appropriate if it is approved by the local Health Authority.

8.1.8. Progressive Multifocal Leukoencephalopathy (Rituximab)

John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, has been observed in subjects treated with rituximab. Subjects with new onset or changes to preexisting neurologic manifestations should be evaluated for PML. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (eg, muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as "cortical" (eg, aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA). Study treatment should be discontinued in subjects who develop PML. The subject should be referred to a neurologist for the evaluation and treatment of PML.

8.2. Prohibited Concomitant Medications and Procedures

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary or should be used with caution during the study. The sponsor must be notified if a subject receives any of these during the study.

1. Any investigational anticancer therapy;

2. Any concurrent chemotherapy, radiation therapy (except IFRT in Arm D when the subject meets the criteria in Section 3.1.2), immunotherapy, biologic or hormonal therapy for cancer treatment;
3. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable;
4. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers;

   Notes:

   For subjects with bulky disease, systemic symptoms, compressive disease, or rapidly progressing adenopathies, pre-phase treatment with 1 mg/kg/day prednisone, or equivalent, for a maximum of 7 days is permitted prior to Cycle 1 Day 1, at the discretion of the investigator.

   Use of immunosuppressive medications for the management of IP-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.
5. Live attenuated vaccines during the study through 120 days after the last dose of durvalumab and 12 months after last dose of rituximab or until recovery of B-cells, whichever occurs later;
6. Herbal and natural remedies are to be avoided.
7. Based intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

8.2.1. Prohibited Concomitant Medications for Arm B Only (Ibrutinib)

1. Concomitant anticoagulation with warfarin or other vitamin K antagonists is prohibited within 7 days prior to study entry, while on treatment with ibrutinib, and until 7 days after the last dose of ibrutinib. Alternative, anticoagulation can be given with caution. Investigators should consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and postsurgery depending upon the type of surgery and the risk of bleeding;
2. Strong and moderate inhibitors of CYP3A should be avoided. For strong CYP3A inhibitors used for short-term, ibrutinib should be interrupted during the duration of the inhibitor use. If a moderate inhibitor must be used, ibrutinib dose may be reduced. CYP3A inhibitors that are needed chronically are prohibited. In addition, grapefruit and Seville oranges should be avoided;
3. Strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin and St. John's Wort) should be avoided.

8.2.2. Prohibited Concomitant Medications for Arm C Only (Bendamustine)

1. Caution should be used, or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors (eg, fluvoxamine, ciprofloxacin and other fluoroquinolones, amiodarone, ticlopidine, efavirenz, cimetidine) or inducers (eg, omeprazole, rifampin);
2. Caution should be used, or alternative treatments considered if concomitant treatment with allopurinol is needed as allopurinol may enhance the adverse effect (specifically, the risk of severe skin reactions) of bendamustine.

8.3. Required Concomitant Medications and Procedures

8.3.1. Hepatitis B Virus Reactivation Prophylaxis

In subjects with prior HBV infection, HBV reactivation may occur during or after rituximab, bendamustine or ibrutinib treatment even if HBV-DNA is undetectable. Reactivation cases have also been reported from worldwide postmarketing experience with lenalidomide and are considered to be at least possibly related to lenalidomide.

For subjects with evidence of prior HBV exposure (positive for anti-HBs and/or anti-HBc with or without detectable HBV-DNA), liver disease experts should be consulted before start of rituximab, bendamustine, ibrutinib or lenalidomide treatment. Such subjects should be monitored for clinical and laboratory signs (eg, elevation in liver enzymes) of hepatitis and/or HBV reactivation during and following rituximab, bendamustine, ibrutinib or lenalidomide treatment and managed following local medical standards to prevent HBV reactivation. In case of any suspicion for HBV reactivation, HBV DNA should be repeated at any time during the study in consultation with a hepatologist.

In subjects who develop HBV reactivation during the study treatment, the study treatment should be immediately discontinued. In subjects who develop HBV reactivation during or after the study treatment, appropriate HBV treatment (eg, lamivudine) should be instituted as per local medical practice and locally approved product/prescribing information.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This Phase 1/2 study consists of a dose finding part (Phase 1), a dose confirmation part (Phase 1), and a dose expansion part (Phase 2).

The primary objective of the dose finding part is to assess the safety and tolerability of durvalumab when given in combination with lenalidomide ± rituximab; ibrutinib; or bendamustine ± rituximab to determine the RP2D of each combination in subjects with lymphoma or CLL.

The primary objective of the dose confirmation part is to assess the safety and explore the preliminary efficacy of durvalumab as monotherapy and when given in combination with lenalidomide ± rituximab; ibrutinib; or bendamustine ± rituximab at the RP2D in subjects with lymphoma or CLL.

The primary objective of the dose expansion part is to further evaluate the preliminary efficacy of durvalumab when given in combination with lenalidomide ± rituximab; ibrutinib; or bendamustine ± rituximab in subjects with lymphoma or CLL.

Arm A (durvalumab plus lenalidomide with or without rituximab) is discontinued to the enrollment of new subjects. 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.

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. As a result, 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.

On 16 Sep 2017, following the Partial Clinical Hold, Celgene together with AstraZeneca/MedImmune confirmed the decision to close the enrollment of the study. 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.

9.2. Study Population Definitions

The statistical analysis populations are defined as follows; the decision on 16 Sep 2017, following the Partial Clinical Hold alters the definition of population by not considering the dose expansion part.

- Safety Population (for the dose finding part, the dose confirmation part, and the dose expansion part): All subjects who take at least one dose of IP. Reporting done on Safety Population will be done against actual treatment received.
- DLT Evaluable Population (for the dose finding part): In Arms A, B, and C, all subjects who take at least one dose of IP and completed the DLT evaluation through

the end of Cycle 1, or the subjects who take at least one dose of IP and have experienced at least one DLT prior to completion of Cycle 1. Reporting done on DLT Evaluable Population will be done against actual treatment received.

- Efficacy Evaluable Population (for the dose confirmation part and the dose expansion part): All subjects who complete at least one cycle of their assigned treatment, have baseline and at least one post-baseline tumor response assessment. Reporting done on Efficacy Evaluable Population will be done against planned treatment.
- Pharmacokinetic (PK) Population: All subjects who receive at least one dose of IP and have at least one measurable plasma concentration. Reporting done on PK Population will be done against actual treatment received.
- Biomarker Evaluable Population: All subjects who receive at least one dose of IP and have at least one non-missing biomarker assessment, excluding the disqualified assessments. Reporting done on Biomarker Evaluable Population will be done against actual treatment received.

9.3. Sample Size and Power Considerations

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. As a result, 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.

On 16 Sep 2017, following the Partial Clinical Hold, Celgene together with AstraZeneca/MedImmune confirmed the decision to close the enrollment of the study. 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

The original sample size for the dose finding part, the dose confirmation part, and the dose expansion part is described in the subsections below. There is a maximum of 60 (DLT evaluable) subjects required for the dose finding part, a maximum of approximately 100 subjects for the dose confirmation part, and a maximum of approximately 105 subjects for the dose expansion part, thus, a total of approximately 265 subjects for the entire study.

9.3.1. Dose Finding Part (Phase 1)

There are 3 treatment arms in the dose finding part, ie, 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 MTD and RP2D for each treatment arm. The total sample size for the dose finding part ranges from 15 to 60 (DLT evaluable) 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.

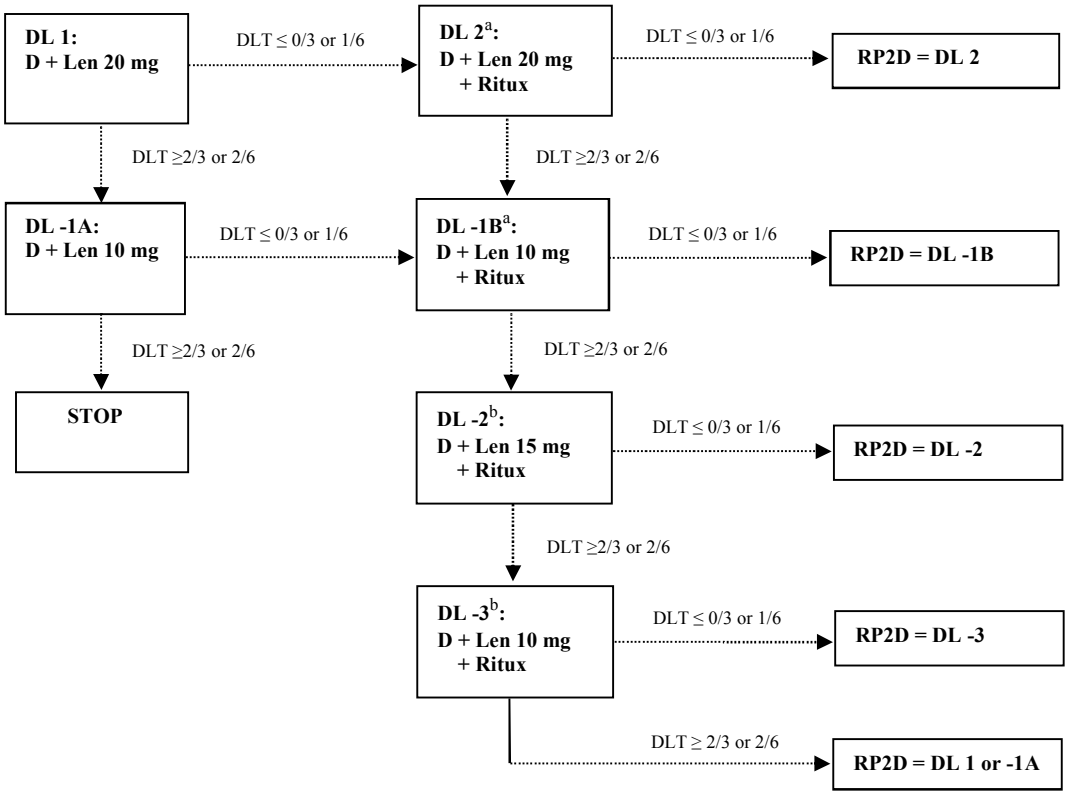
9.3.1.1. Arm A (Discontinued to the Enrollment of New Subjects)

Subjects with R/R B-cell NHL will be enrolled into Arm A according to the chart below. 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).

Figure 4: Arm A Dose Finding Flow Chart



Abbreviations: D = durvalumab; DL = dose level; DLT = dose limiting toxicity; Len = lenalidomide; Ritux = rituximab.

[a] DL 2 and -1B: Rituximab Schedule 1, rituximab every week in Cycle 1 (Days 2, 8, 15, 22) and on Day 1 of every 28-day cycle from Cycles 2 through 5.

[b] DL -2 and DL -3: Rituximab Schedule 2, rituximab on Day 2 of Cycle 1 and on Day 1 of every 28-day cycle from Cycles 2 through 8.

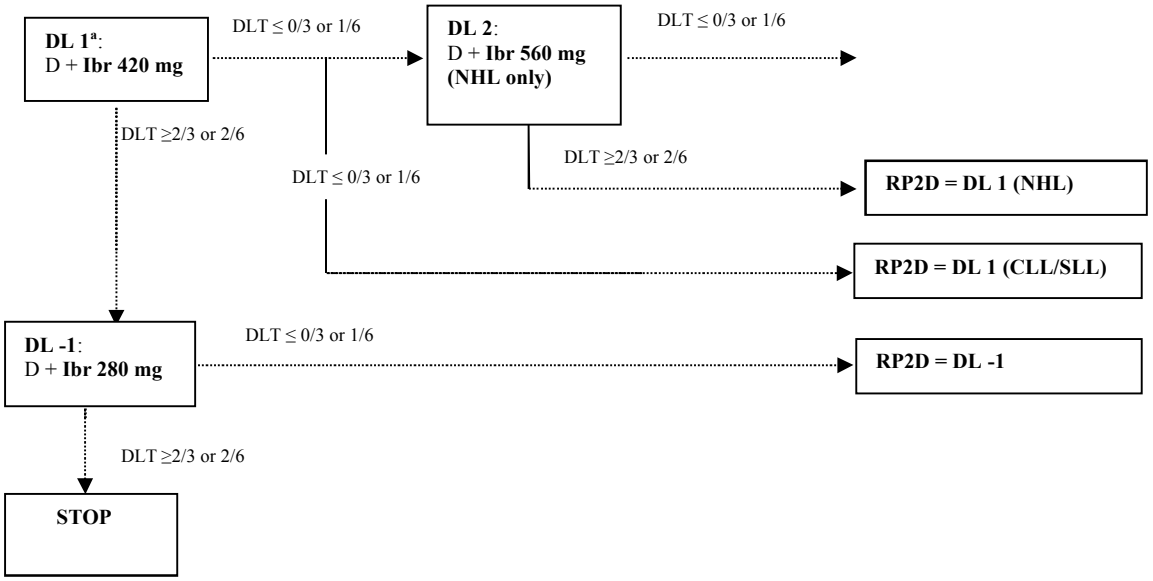
9.3.1.2. Arm B

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

- DL1 → DL2
- 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).

Figure 5: Arm B Dose Finding Flow Chart



Abbreviations: CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; D = durvalumab; DL = dose level; DLT = dose limiting toxicity; Ibr = ibrutinib; NHL = non-Hodgkin lymphoma.

[a] This dose level will be the highest dose level tested in subjects with CLL/SLL before opening CLL/SLL dose confirmation cohorts.

9.3.1.3. Arm C

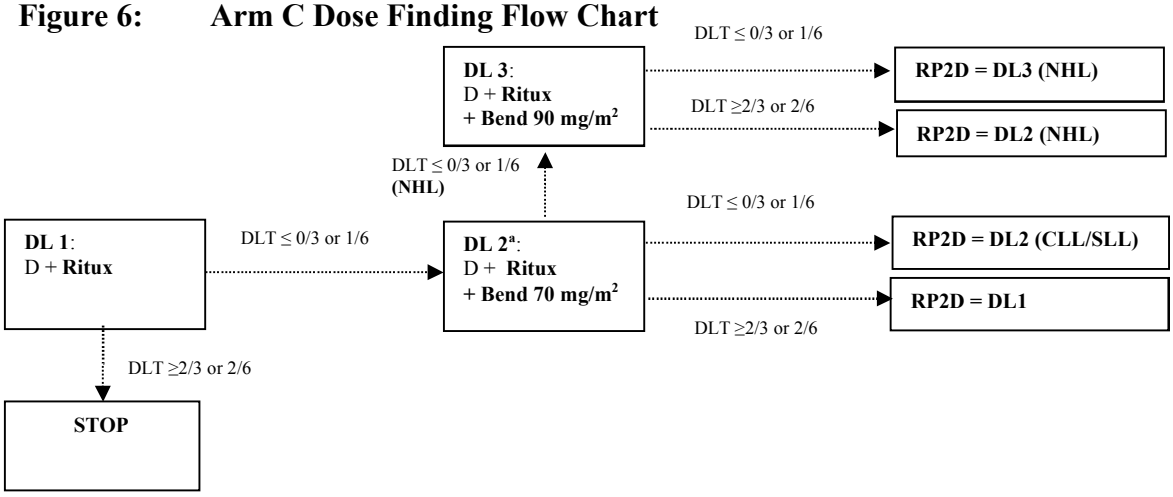
Subjects with R/R B-cell NHL or CLL/SLL will be enrolled into Arm C according to the chart below. There are 2 potential dose finding paths:

DL1 → DL2

DL1 → DL2 → DL3

The sample size required for Arm C ranges from a minimum of 3 subjects (1 dose levels with 3 subjects per dose level) to a maximum of 18 subjects (3 dose levels with 6 subjects per dose level).

Figure 6: Arm C Dose Finding Flow Chart



Abbreviations: Bend = bendamustine; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; D = durvalumab; DL = dose level; DLT = dose limiting toxicity; NHL = non-Hodgkin lymphoma; Ritux = rituximab.
[a] This dose level will be the highest dose levels tested in subjects with CLL/SLL before opening CLL/SLL dose confirmation cohorts.

9.3.2. Dose Confirmation Part (Phase 1)

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 rules by targeting with 10 subjects a probability of less than 20% of observing a certain number of responses or fewer on the stopping rules (eg, for Arm C, histology R/R CLL/SLL, given expected ORR is 65%, the 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 rules described in Table 34 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 are 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.

Table 34: Dose Confirmation Part Stopping Rules for Efficacy

Treatment Arm	Subject Histology Cohort	Stopping Rules	Justification
A **Discontinued to the enrollment of new subjects**	R/R FL (N = 10)[a]	≤ 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)[a]	≤ 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%.
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 lymphoma; MCL = mantle cell lymphoma; N = number of subjects; ORR = overall response rate; R/R = relapsed/refractory; SLL= small lymphocytic lymphoma.

[a] Arm A dose confirmation and dose expansion cohorts are discontinued and will not enroll new subjects.

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 in each arm/cohort in the dose finding part.

9.3.3. Dose Expansion Part (Phase 2)

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

The total sample size for the dose expansion part is estimated to be approximately 105 subjects in Arms A, B, and C as described in the Table 24. The final number of subjects will also depend on the number of arms/cohorts in which the RP2D can be confirmed from the dose confirmation part.

Table 35: Dose Expansion Part Sample Size

Treatment Arm	Subject Histology Cohort
A **Discontinued to the enrollment of new subjects**	R/R FL (N = 15)[a]
	R/R DLBCL (N = 15)[a]
B	R/R CLL (N = 15)
	R/R MCL (N = 15)
C	R/R CLL (N = 15)
	R/R FL (N = 15)
	R/R DLBCL (N = 15)

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete response; FL = follicular lymphoma; DLBCL= diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; N = number of subjects; R/R = relapsed/refractory

[a] Arm A dose confirmation and dose expansion cohorts are discontinued and will not enroll new subjects.

For arm/cohort selected to continue in the dose expansion part, 15 additional subjects will be recruited. In order to make use of all available data, the data of 15 subjects in the dose expansion part and the data of 10 subjects in the dose confirmation part for a particular histology will be pooled together for treatment efficacy evaluation. A total of approximately 25 subjects in a particular treatment arm and subject histology cohort will provide moderate estimate of the response rate with 95% confidence interval (CI) no wider than ± 20%, considered as moderate risk level for decision making and appropriate level of information in order to power potential future Phase 3 studies.

9.4. Background and Demographic Characteristics

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by MedDRA system organ class and preferred term.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both Treatment and Follow-up Periods. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

In the dose confirmation part (dose expansion part was not opened as originally planned), treatment efficacy will be evaluated by different histology cohorts for each treatment arm. For each subject in Arms A (indolent NHL: FL or MZL), C, D, treatment efficacy will be evaluated from his/her last durvalumab dose until 24 months; in Arms A (aggressive NHL) and B, treatment efficacy will be evaluated from his/her last durvalumab dose until 24 months after their last durvalumab dose or their disease progression, whichever date occurs later.

All efficacy evaluable subjects will be included for efficacy analysis.

Efficacy analysis will be performed for particular treatment arm and subject histology cohort by combining data from the dose confirmation part only as the dose expansion part was not opened.

For lymphoma subjects, response evaluation will be based on IWG Response Criteria for Malignant Lymphoma (the Lugano Classification) (Cheson 2014). The overall response rate (ORR) is defined as the percent of subjects with best response of CR or PR. Duration of response (DoR) is defined for responders only as the time from the first response (CR or PR) to disease progression or death.

For CLL subjects, response evaluation will be based on IWCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008), as modified by (Hallek, 2012) and (Hallek, 2013). The overall response rate (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). Duration of response (DoR) is defined for responders only as the time from the first response (CR, CRi, nPR, PR, or PRL) to disease progression or death.

The response rate based on the best response during durvalumab treatment as well as during the entire efficacy evaluation period will be summarized by subject histology cohort for each treatment arm.

For subjects with response but no progression, or death, duration of response will be censored at the last date that the subject was known to be progression free. Duration of response will be analyzed using the Kaplan-Meier method. Median DoR along with two-sided confidence interval will be provided for each treatment arm and subject histology cohort.

Progression-free survival (PFS) is calculated as the time from first IP dose to the first documented progression or death due to any cause during the entire efficacy evaluation period. For subjects with no progression or death, PFS will be censored at the last date that 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.

Overall survival (OS) is calculated as the time from first IP dose to the date of death due to any cause. For subjects who did not die, OS will be censored at the last date that the subject was known to be alive. OS will be analyzed similarly to PFS and DoR.

9.7. Safety Analysis

Safety analysis will include all subjects in the Safety population.

Investigational product exposure will be summarized for each treatment arm and histology cohort including duration of investigational product, total dose taken, and dose reductions.

Adverse events, vital sign measurements, clinical laboratory measurements, physical examination and concomitant medications will be summarized by treatment arm and histology cohort.

Adverse events will be coded according to Medical Dictionary for Drug Regulatory Activities (MedDRA) and classified using the NCI CTCAE. The incidence rates of AEs will be tabulated by system organ class and preferred term. The incidence of AEs will also be tabulated by severity within each system organ class and preferred term. The most severe grade of each preferred terms and adverse events of special interest (see Section 10.7) for a subject will be utilized for summaries of AEs by NCI CTCAE grade.

Subsets of AEs to be summarized include AESIs, SAEs, suspected treatment-related AEs, and AEs that resulted in withdrawal of investigational product.

All AEs with corresponding attributes will be displayed in a by-subject listing. AEs leading to death or to discontinuation from treatment, events classified as NCI CTCAE Grade 3 or higher, suspected treatment-related events, and SAEs will also be displayed in separate by-subject listings.

Laboratory data will be graded according to NCI CTCAE severity grade. The frequencies of the worst severity grade observed during treatment will be displayed in cross-tabulations by baseline status for each treatment arm and histology cohort.

For variables for which an NCI CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges pretreatment and during treatment will be summarized by treatment and histology cohort.

Change from baseline will be descriptively summarized at each post-baseline visit by treatment arm and histology cohort.

Laboratory shift tables will be produced by treatment arm.

9.8. Interim Analysis

No formal interim analysis is planned for this study.

Following the decision to stop the follow-up data collection, no additional analyses will be performed after the primary analysis completion.

9.9. Other Topics

The PK and biomarker analysis will be specified in separate analysis plan.

9.9.1. Steering Committee

The conduct of this trial will be overseen by a global scientific steering committee (GSSC), presided over by the coordinating Principal Investigator(s) and if possible the lead investigators of each treatment arm from countries participating in this study. The GSSC will serve in an advisory capacity to the Sponsor. Operational details for the GSSC will be detailed in a separate GSSC charter.

9.9.2. Exploratory Analysis

Possible relationships between molecular/cellular characteristics and safety and efficacy variables may be explored, as appropriate.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.4 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for durvalumab, lenalidomide, ibrutinib, rituximab, bendamustine, or local IFRT overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the investigator from the time the subject signs informed consent until 90 days from the last dose of durvalumab or 28 days from the last dose of any IP (ie, lenalidomide, ibrutinib, rituximab, bendamustine, or local IFRT), whichever occurs later, as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to study treatment. AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

Following completion of the primary analysis (data cutoff date 06 Mar 2019), AEs and SAEs are no longer required to be collected in the CRFs.

For subjects still receiving ibrutinib on-study, investigators will continue to record all AEs/ SAEs in the subject's source documents and report SAEs to Celgene Drug Safety, as well as those SAEs made known to the investigator at any time thereafter, that are suspected of being related to study treatment.

10.2. Evaluation of Adverse Events

A qualified investigator will evaluate all AEs as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- results in death;
- is life-threatening (ie, in the opinion of the investigator, the subject is at immediate risk of death from the AE);
- requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- is a congenital anomaly/birth defect; or
- constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- an elective treatment of or an elective procedure for a preexisting condition, unrelated to the studied indication that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship to the study treatment, action taken regarding the study treatment, and outcome.

10.2.2. Severity/Intensity

For both AEs and SAEs, the investigator must assess the severity/ intensity of the event.

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active version of the NCI CTCAE Version 4.03 with the exception of TLS (Cairo, 2004; Appendix D) and laboratory abnormalities as recommended by the IWCLL guidelines for the diagnosis and treatment of CLL (Hallek, 2008; Appendix E); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Adverse events that are not defined in the NCI CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death]

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The investigator must determine the relationship between the administration of the IP(s) and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	A causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	There is a **reasonable possibility** that the administration of IP(s) caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP(s) and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or

- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

The exposure of any pregnant female (eg, caregiver, pharmacist, study coordinator or monitor) to lenalidomide is also an immediately reportable event.

10.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 90 days after the last dose of durvalumab, ibrutinib, or bendamustine; 12 months after the last dose of rituximab; or 28 days after last dose of lenalidomide, whichever occurs later, are considered immediately reportable events.

Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP (ie, lenalidomide or ibrutinib) to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to any IP should also be reported to Celgene Drug Safety by

facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 90 days from the last dose of durvalumab or 28 days from the last dose of any other study treatment [ie, lenalidomide, ibrutinib, rituximab, bendamustine, or local IFRT], whichever occurs later) or any SAE made known to the investigator at any time thereafter that are suspected of being related to IP or participation in the study (eg, a study-related procedure). In case of local regulations and/or requirements, any SAE made known to the investigator beyond the protocol-defined safety follow-up period above may be reported to Celgene Drug Safety even if not suspected of being related to IP or participation in the study (eg, a study-related procedure)

Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Following completion of the primary analysis (data cutoff date 06 Mar 2019), AEs and SAEs are no longer required to be collected in the CRFs.

For subjects still receiving ibrutinib on-study, investigators will continue to record all AEs/ SAEs in the subject's source documents and report SAEs to Celgene Drug Safety, as well as those SAEs made known to the investigator at any time thereafter, that are suspected of being related to study treatment.

Where required by local legislation, the investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than 5 business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to durvalumab or lenalidomide based on the Investigator's Brochure.

In the US, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IPs (ie, rituximab, bendamustine, or ibrutinib) based on the EU Summary of Product Characteristics (SmPC). Any SAE that is suspected of being be related to local IFRT alone will not be assessed for expectedness or reported in an expedited manner.

Celgene or its authorized representative shall notify the investigator of the following information (in Japan, Celgene KK shall notify the Heads of the Institutes in addition to the investigators):

- Any AE suspected of being related to the use of IP(s) in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity;
- In Japan, measures taken in foreign countries to ensure subject safety, study reports that indicate potential risk of cancer, etc, or annual SAE report according to the local regulations.

Where required by local legislation, the investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 14.3 for record retention information).

10.7. Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to the understanding of durvalumab and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or nonserious The rapid reporting of

AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of durvalumab.

Adverse event of special interest for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the investigator has any questions in regards to an adverse event (AE) being an imAE, the investigator should promptly contact the sponsor's medical monitor.

Further information on these AESI (eg, presenting symptoms) can be found in the current version of the Durvalumab Investigator's Brochure.

10.7.1. Second Primary Malignancies (SPMs)

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in and must be considered as "Important Medical Events" if no other serious criteria apply. This includes any second primary malignancy, regardless of causal relationship to IP (study drugs), occurring at any time for the duration of the study, from the time of signing the ICF for at least 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 in the study, whichever is the later date for an individual subject,

as well as those SPMs made known to the investigator at any time thereafter that are suspected of being related to any IP.

These events must also be documented in the appropriate page(s) of the CRF (ie, AE and SPM CRF) and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, x-rays, CT scans, etc).

Following completion of the primary analysis (data cutoff date 06 Mar 2019), SPMs will no longer be collected in the CRFs. For all subjects, investigators will continue to record SPMs in the subject's source documents and report SPM events to Celgene Drug Safety.

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

Any of the following events are considered sufficient reasons for discontinuing a subject from the IPs:

- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow-up
- Disease progression
- Pregnancy
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the investigator may contact the sponsor's medical monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

Any of the following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization medical monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physicians or medical monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all investigators who in turn will select their staff.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The investigator should maintain a list of Sub-s and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide investigators with a summary of the results that is written for the lay person. The investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The investigator must keep a record of all communication with the IRB/EC and, if applicable, between a coordinating investigator and the IRB/EC. This statement also applies to any communication between the investigator (or coordinating investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

There will be no analysis of data generated after the primary analysis data cutoff date 06 Mar 2019. Any data generated after this data cutoff date will be maintained in the source documents and will not need to be entered in the CRFs.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

There will be no analysis of data generated after the primary analysis data cutoff date 06 Mar 2019. Any data generated after this data cutoff date will be maintained in the source documents and will not need to be entered in the CRFs.

14.3. Record Retention

Essential documents must be retained by the investigator according to the period of time outlined in the Clinical Trial Agreement. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the investigator, Celgene, and their authorized representative(s);
- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;

- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The investigator must obtain approval in writing from Celgene prior to destruction of any records. If the investigator is unable to meet this obligation, the investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the investigator and the staff at a study initiation visit and/or at an investigators' meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the investigator. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA) and company authorized representatives. The investigator should make every effort to be available for the audits and/or inspections. If the investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, contribution in essential correlative studies, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

17. REFERENCES

Almo SC, Guha C. Considerations for combined immune checkpoint modulation and radiation treatment. Radiat Res 2014182(2):230-8.

Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372(4):311-9.

Armitage JO. Treatment of non-Hodgkin's lymphoma. N Engl J Med 1993;328(14):1023-30.

Baitsch L, Fuertes-Marraco SA, Legat A, Meyer C, Speiser DE. The three main stumbling blocks for anticancer T-cells. Trends Immunol 2012;33(7):364-72.

Bendeka® (bendamustine) [Package Insert]. North Wales, PA: Teva Pharmaceuticals; 2016. Available from: http://bendeka.com/Pdf/PrescribingInformation.PDF. Accessed February 08, 2017.

Benson DM Jr, Bakan CE, Mishra A, Hofmeister CC, Efebera Y, Becknell B, et al. The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody. Blood 2010;116(13):2286-94.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56(5):739-45.

Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28(19):3167-75.

Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455-65.

Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127(1):3-11.

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, Publish Date: August 9, 2006. Available from: http://ctep.cancer.gov.

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, NCI, NIH, DHHS, Publish Date: May 28, 2009. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol 2014;32(27):3059-68.

Cheson BD, Ansell S, Schwarts L, Gordon LI, Advani R, Jacene HA, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood 2016;128(21):2489-2496.

Clemente CG, Mihm MC Jr, Bufalino R, Zurrida S, Collini P, Cascinelli N. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. Cancer 1996;77(7):1303-10.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Crespo J, Sun H, Welling TH, Tian Z, Zou W. T-cell anergy, exhaustion, senescence, and stemness in the tumor microenvironment. Curr Opin Immunol 2013;25(2):214-21.

Coupland SE. The challenge of the microenvironment in B-cell lymphomas. Histopathology. 2011;58(1):69-80.

Czuczman MS, Koryzna A, Mohr A, Stewart C, Donohue K, Blumenson L, et al. Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma. J Clin Oncol 2005;23(4):694-704.

Dieu-Nosjean, MC, Antoine, M, Danel, C, Heudes, D, Wislez, M, Poulot, V, et al. Long-term survival for patients with non-small-cell lung cancer with intratumoral lymphoid structures. J Clin Oncol 2008;26(27):4410-7.

Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.

Fairman D, Narwal R, Liang M, Robbins PB, Schneider A, Chavez C, et al. Pharmacokinetics of MEDI4736, a fully human anti-PD-L1 monoclonal antibody, in patients with advanced solid tumors [abstract]. J Clin Oncol, 2014 ASCO Annual Meeting Abstracts. 2014;32(suppl 5): Abstract# 2602.

Fischer K, Cramer P, Busch R, Stilgenbauer S, Bahlo J, Schweighofer CD, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011; 29 (26):3559-66.

Food and Drug Administration (FDA). Guidance for industry: drug-induced liver injury: premarketing clinical evaluation. July 2009.

Fowler N, Neelapu SS, Hagemeister F, McLaughlin P, Kwak LW, Romaguera JE, et al. Lenalidomide plus Rituximab for untreated indolent lymphoma: final results of phase II study. 54th ASH Annual Meeting and Exposition; December 2012; Abstract 901.

Fowler NH, Davis RE, Rawal S, Nastoupil L, Hagemeister FB, McLaughlin P, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. Lancet Oncol (England) 2014; 15:1311–8.

Galon, J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pages C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313(5795):1960-4.

Gooden MJ, De Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systemic review with meta-analysis. Br J Cancer 2011;105(1):93-103.

Gordon MS, Hamid O, Powderly J, Anderson M, Fine G, Mokatrin A, et al. A phase I study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors [abstract]. American Association for Cancer Research 2013 Annual Meeting.2013 Apr 6-10; Washington, DC; USA: Abstract LB-288.

Gorgun G, Samur MK, Cowens KB, Paula S, Bianchi G, Anderson JE, et al. Lenalidomide Enhances Immune Checkpoint Blockade-Induced Immune Response in Multiple Myeloma. Clin Cancer Res 2015;21(20);4607-18.

Gribben JG, Fowler N, Morschhauser F. Mechanisms of Action of Lenalidomide in B-Cell Non-Hodgkin Lymphoma. J Clin Oncol 2015;33(25):2803-11.

Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute -Working Group 1996 guidelines. Blood 2008;111(12):5446-56.

Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute -Working Group 1996 guidelines. Blood 2008;111(12):5446-56. E-letter: Response assessment in chronic lymphocytic leukemia treated with novel agents causing an increase of peripheral blood lymphocytes. June 2012.

Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute -Working Group 1996 guidelines. Blood 2008;111(12):5446-56. E-letter: Clarification of IwCLL criteria for a partial response to therapy.

Harzstark AL, Small EJ. Castrate-resistant prostate cancer: therapeutic strategies. Expert Opin Pharmacother 2010;11(6):937-45.

Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515(7528):563-7.

Higgs BW, Robbins PB, Blake-Haskins JA, Zhu W, Morehouse C, Brohawn PZ, et al. High tumoral IFNγ mRNA, PD-L1 protein, and combined IFNγ mRNA/PD-L1 protein expression associates with response to durvalumab (anti-PD-L1) monotherapy in NSCLC patients [abstract]. Presented at: The European Cancer Congress 2015. 2015 25-29 September; Vienna; Austria: Abstract# 15LBA.

Higgs BW, Morehouse CA, Streicher KL, Rebelatto MC, Steele K, Jin X, et al. Baseline tumoral IFNγ mRNA and PD-L1 protein expression associated with overall survival in durvalumab treated NSCLC patients [abstract]. Presented at: The 2016 ASCO Annual Meeting. 2016 3-7 June; Chicago; IL, USA: Abstract # 3036.

Hirano F, Kaneko K,Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by Monoclonal Antibodies Potentiates Cancer Therapeutic Immunity. Cancer Res 2005;65(3):1089-96.

Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37 Suppl 1:48-53.

Ibrahim R, Stewart S, Shalabi A. PD-L1 blockade for cancer treatment. Seminars in Oncology 2015; 42 (3):474-83.

Imbruvica® (ibrutinib) [Package Insert]. Sunnyvale, CA: Pharmacyclics; 2013. Available from: http://www.imbruvica.com/docs/librariesprovider3/default-document-library/prescribing_information.pdf?sfvrsn=2. Accessed March 09, 2017.

Imbruvica® (ibrutinib) [Summary of Product Characteristics]. Beerse, Belgium: Janssen-Cilag International NV; 2014. Available from: http://www.medicines.org.uk/emc/medicine/29383. Accessed March 09, 2017.

Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A. 2002;99(19):12293-7.

Kearl TJ, Jing W, Gershan J, Johnson BD. Programmed death receptor-1/programmed death receptor ligand-1 blockade after transient lymphodepletion to treat myeloma. J Immunol 2013;190(11):5620-8.

Leonard JP, Jung SH, Johnson J, Bartlett NL, Blum KA, Czuczman M, et al. Lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance).

Leoni LM, Bailey B, Reifert J, Bendall HH, Zeller RW, Corbeil J, et al. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. Clin Cancer Res 2008;14(1):309-17.

Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, et al. Preliminary results of a phase I study of nivolumab (BMS-936558) in patients with relapsed or refractory lymphoid malignancies. Blood 2014;124(21): ASH Abstract 291.

Levact ® [Summary of Product Characteristics]. Dublin, Ireland: Mundipharma Pharmaceuticals Limited - Formerly Napp Laboratories; 2014. Available from: http://www.medicines.ie/medicine/14828/SPC/Levact+25mg+and+100+mg++powder+for+concentrate+for+solution+for+infusion/. Accessed March 09, 2017.

Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7(11):1630-6.

Luptakova K, Rosenblatt J, Glotzbecker B, Mills H, Stroopinsky D, Kufe T, et al. Lenalidomide enhances anti-myeloma cellular immunity. Cancer Immunol Immunother 2013;62(1):39-49.

MabThera® (rituximab) [Summary of Product Characteristics]. Grenzach-Wyhlen, Germany: Roche Pharma AG; 2014. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf. Accessed March 09, 2017.

McClanahan F, Riches JC, Miller S, Day WP, Kotsiou E, Neuberg D, et al. Mechanisms of PD-L1/PD-1-mediated CD8 T-cell dysfunction in the context of aging-related immune defects in the Eμ-TCL1 CLL mouse model. Blood 2015;126(2):212-21.

McClanahan F, Hanna B, Miller S, Clear AJ, Lichter P, Gribbern JG, et al. PD-L1 checkppoint blockade prevents immune dysfunction and leukemia development in a mouse model of chronic lymphocytic leukemia. Blood 2015;126(2):203-11.

Moskowitz CH, Ribrag V, Michot J-M, Martinelli G, Zinzani PL, Gutierrez M, et al. PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: preliminary results from a phase 1b study (KEYNOTE-013). Blood 2014;124(21): ASH Abstract 290.

Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon-α monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet. 2013;52(11):1017-27. Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275-84.

Novak M, Prochazka V, Turcsanyi P, Papajík T. Numbers of CD8+PD-1+ and CD4+PD-1+ Cells in Peripheral Blood of Patients with Chronic Lymphocytic Leukemia Are Independent of Binet Stage and Are Significantly Higher Compared to Healthy Volunteers. Acta Haematol. 2015;134(4):208-4.

Oganesyan V, Gao C, Shirinian L, Wu H, Dall'Acqua WF. Structural characterization of a human Fc fragment engineered for lack of effector functions. Acta Crystallogr D Biol Crystallogr. 2008;64(6):700-4.

Ohmachi K, Niitsu N, Uchida TJ, Kim SJ, Ando K, Takahashi N, 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;31(17):2103-9. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.

Okudaira, K, Hokari, R, Tsuzuki, Y, Okada, Y, Komoto, S, Watanabe, C, et al. Blockade of B7-H1 or B7-DC induces an antitumor effect in a mouse pancreatic cancer model. Int J Oncol 2009;35(4):741-9.

Postow MA. Managing immune checkpoint blocking antibody side effects. In: Dizon DS, Pennel N, Pickell L, editors. The American Society of Clinical Oncology 2015 Educational Book. 51st Annual Meeting; 2015 May 29-Jun 2; Chicago, IL; vol. 35. Alexandria (VA): American Society of Clinical Oncology; 2015. p.76-83. Available from: http://www.asco.org/edbook.

Ramsay AG, Evans R, Kiaii S, Svensson L, Hogg N, Gribben JG. Chronic lymphocytic leukemia cells induce defective LFA-1-directed T-cell motility by altering Rho GTPase signaling that is reversible with lenalidomide. Blood 2013;121(14):2704-14.

Revlimid® (lenalidomide) [Prescribing Information]. Summit, NJ: Celgene Corporation; 2015. http://www.celgene.com/content/uploads/revlimid-pi.pdf. Accessed March 09, 2017

Revlimid® (lenalidomide) [Summary of Product Characteristics]. Switzerland: Celgene Europe Limited; 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000717/WC500056018.pdf. Accessed March 09, 2017.

Reynders K, Illidge T, Siva S, Chang JY, De Ruysscher D. The abscopal effect of local radiation therapy: using immunotherapy to make a rare event clinically relevant. Cancer Treat Rev. 2015;41(6):503-510.

Rituxan [package insert]. South San Francisco, CA: Genentech, Inc;2013.

Rituxan® (rituximab) [Prescribing Information]. South San Francisco, CA: Genentech; 2014. http://www.gene.com/download/pdf/rituxan_prescribing.pdf. Accessed March 09, 2017.

Rizvi N, Brahmer J, Ou SH, Khleif SN, Hwu WJ, Gutierrez M, et al. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC). The ASCO Annual Meeting; 2015. Chicago, IL: USA; Poster #8032.

Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364(26):2517-26.

Rossille D, Gressier M, Damotte D, Maucort-Boulch D, Pangault C, Semana G, et al. High level of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive diffuse large B-Cell lymphoma: results from a French multicenter clinical trial. Leukemia 2014;28(12)2367-75.

Rummel MJ, Al-Batran SE, Kim S-Z, Welslau M, Hecker R, Kofahl-Krause D, 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(15):3383-89.

Sagiv-Barfi I, Kohrt HE, Czerwinski DK, Ng PP, Chang BY, Levy R. Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK. Proc Natl Acad Sci U S A 2015;112(9):E966-72.

Salvi F, Miller MD, Grilli A, Giorgi R, Towers AL, Morichi V, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008a;56(10):1926-31.

Salvi F, Miller M, Towers A, Grilli A, Morichi V, Giorgi R, et al. Manual of guidelines for scoring the modified cumulative illness rating scale (CIRS). J Am Geriatr Soc 2008b;56.

Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al; HAEMACARE Working Group. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010;116(19):3724-34.

Segal NH, Hamid O, Hwu WJ, Massard C, Butler M, Antonia S, et al. A phase 1 multi-arm dose-expansion study of the anti-programmed cell death-ligand-1 (PD-L1) antibody MEDI4736: Preliminary data. European Society of Medical Oncology (ESMO) Annual Meeting. 2014 Sep 26-30; Madrid, Spain: Abstract #5888.

Segal NH, Ignatius SH, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma

of the head and neck (SCCHN) expansion cohort. American Society of Oncology (ASCO) Annual Meeting. 2015 Jul 31-Aug 1. Chicago (IL), USA; 2015. Abstract #3011.

Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2015. CA Cancer J Clin 2015; 65(1):5-29.

Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Hematological Malignancy Research Network. Br J Cancer 2011;105(11):1684-92. Storer BE. Design and analysis of phase I clinical trials. Biometrics 1989:45(3):925-37.

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. (Eds). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC Press, Lyon 2008.

Teng F, Kong L, Meng X, Yang J, Yu J. Radiotherapy combined with immune checkpoint blockade immunotherapy: Achievements and challenges. Cancer Lett2015;365((1):23-9.

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443-54.

Topalian SL, Sznol M, Brahmer JR, McDermott DF, Smith DC, Gettinger SN, et al. Nivolumab (anti-PD-1; BMS-936558; ONO4538) in patients with a dvanced solid tumors: survival and long-term safety in a phase 1 trial [abstract]. Presented at: The 2013 Americal Society of Clinical Oncology Annual Meeting. 2013 May 31-June 4; Chicago, IL; USA: Abstract # 3002.

Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568-71.

Treanda ® (bendamustine) [Prescribing Information]. Northwales, PA: Celphalon, Inc., wholly owned subsidiary of Teva Pharmaceutical Industries Ltd, or its affiliates; 2015. Available from: http://www.treanda.com/ PDF/ TREANDA_final_PI.pdf. Accessed March 09, 2017.

Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012-24.

Wang L, Qian J, Lu Y, Li H, Bao H, He D, et al. Immune evasion of mantle cell lymphoma: expression of B7-H1 leads to inhibited T-cell response to and killing of tumor cells. Haematologica 2013;98(9):1458-66.

Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30 (21):2691-7.

Westin JR, Chu F, Zhang M, Fayad LE, Kwak LW, Fowler N, et al. Safety and activity of PD-1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. Lancet Oncol 2014;15(1):69-77.

Wilson WH, Young RM, Schmitz R, Yang Y, Pittaluga S, Wright G, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med 2015;21(8):922-6.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

Yutaka T1, Ito S, Ohigashi H, Naohiro M, Shimono J, Souchi S, et al. Sustained CD4 and CD8 lymphopenia after rituximab maintenance therapy following bendamustine and rituximab combination therapy for lymphoma. Leuk Lymphoma 2015;1-3. http://www.tandfonline.com/doi/full/10.3109/10428194.2015.1026818. Accessed August 14, 2015.

Zhang C, Wu S, Xue X, Li M, Qin X, Li W, et al. Antitumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV. Cytotherapy 2008;10(7):711-9.

Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18-28.

Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008;8(6):467-77.

18. APPENDICES

Appendix A: Table of Abbreviations

Abbreviation or Specialist Term	Explanation
ACTH	Adrenocorticotropic hormone
ADA	Anti drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALK	Anaplastic lymphoma kinase
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
Anti-HBc	Antibody to the hepatitis B core antigen
Anti-HBs	Antibody to the hepatitis B surface antigen
Anti-PD-1	Anti-Programmed Cell Death 1
Anti-PD-L1	Anti-Programmed Cell Death Ligand 1
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	Area under the curve
B-hCG	Beta-human chorionic gonadotropin
BMB	Bone marrow biopsy
BMI	Body mass index
BNP	Brain natriuretic peptide
BPH	Benign prostate hypertrophy
BSA	Body surface area
BTK	Bruton's tyrosine kinase
BUN	Blood urea nitrogen
CBC	Complete blood count
CD	Cluster of differentiation
CHF	Congestive heart failure

Abbreviation or Specialist Term	Explanation
cHL	Classical Hodgkin lymphoma
CI	Confidence interval
CILS	Cumulative illness rating scale
CL	Clearance
c-LDL	Low density lipoprotein cholesterol
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum plasma concentration of drug
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CrCL	Creatinine clearance
CRF	Case report form
CRi	Complete response with incomplete marrow recovery
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
CYP3A	Cytochrome P450, family 3, subfamily A
DILI	Drug induced liver injury
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
DVT	Deep venous thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EOI	End of infusion

Abbreviation or Specialist Term	Explanation
EOT	End of (all) treatment
EOT-D	End of durvalumab treatment
Fc	Fragment crystallizable
FC	Flow cytometry
FCBP	Female (subject) of child bearing potential
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FDG-PET-CT	Integrated FDG-PET with CT
FEV1	Forced expiratory volume in 1 second
FFPE	Formalin fixed paraffin embedded
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
fT3	Free triiodothronine
fT4	Free thyroxine
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony-stimulating factor
GDS	Geriatric Depression Scale
GERD	Gastroesophageal reflux disease
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSSC	Global scientific steering committee
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation

Abbreviation or Specialist Term	Explanation
IEC	Independent Ethics Committee
IFRT	Involved-field radiation therapy
IFNγ	Interferon γ
Ig	Immunoglobulin
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IMiDs®	Immunomodulatory agents
IND	Investigational new drug
INR	International normalized ratio
iNHL	Indolent non-Hodgkin lymphoma
IP	Investigational product
imAE	Immune-mediated adverse events
IRB	Institutional review board
IRT	Integrated response technology
IUD	Intrauterine device
IV	Intravenous
IVIG	Intravenous immune globulin
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWG	International Working Group
JC	John Cunningham
LDH	Lactic dehydrogenase
LLN	Lower limit of normal
LTLS	Laboratory tumor lysis syndrome
mAb	Monoclonal antibody
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MEDI4736	Durvalumab
MI	Myocardial infarction
MM	Multiple myeloma
MMSE	Comprehensive Geriatric Assessment
MRD	Minimum residual disease

Abbreviation or Specialist Term	Explanation
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
N	Number of patients
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NK	Natural killer
nPR	Nodular partial response
NSAID	Non steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NTD	Non-tolerated dose
NYHA	New York Hearth Association
ORR	Overall response rate
OS	Overall survival
PAD	Peripheral arteries disease
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
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
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PO	Per oral
PR	Partial response
PRL	Partial response with lymphocytosis
PRN	Pro re nata; as needed
PTT	Partial thromboplastin time
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks

Abbreviation or Specialist Term	Explanation
QD	Once daily
QIG	Quantitative immunoglobulins
RP2D	Recommended Phase 2 dose
R/R	Relapsed or refractory
RT	Richter's transformation
SAE	Serious adverse event
SLL	Small lymphocytic lymphoma
SmPC	Summary of product characteristics
SOP	Standard operating procedure
sPD-L1	Soluble PD-L1
SPM	Second primary malignancy
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal elimination half-life
Th1	Type 1 T helper
TILs	Tumor-infiltrating lymphocytes
TLS	Tumor lysis syndrome
T_{max}	Time to maximum concentration
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor alpha
TNM	Tumor, nodes, metastasis
TSH	Thyroid stimulating hormone
TURP	Transurethral resection of the prostate
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
V_z/F	Volume of distribution
VTE	Venous thromboembolism
WBC	White blood cell count
WHO	World Health Organization

Appendix B: Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

The guidelines for Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification are outlined in a report (Cheson, 2014).

Table B1: Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies Nonavid disease	PET-CT CT	Increase FDG uptake Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies Nonavid disease	PET-CT CT	Diffuse update, solitary mass, military lesions, nodules > 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies Nonavid disease	PET-CT CT	Diffuse update, mass Nodules
CNS	Signs, symptoms		CT MRI CSF assessment	Mass lesion(s) Leptomeningeal infiltration, mass lesions Cytology, flow cytometry
Other (eg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT[a], biopsy	Lymphoma involvement

Abbreviations: CSF = cerebrospinal fluid; CT = computed tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Table B2: Revised Criteria for Response Assessment

Response and 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 (eg, 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
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 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 sum of perpendicular diameters (SPD) of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed > 50% in length beyond normal
New lesions	None	None

Table B2: Revised Criteria for Response Assessment (Continued)

Response and site	PET-CT based response	CT-based response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic response**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	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 In the setting of splenomegaly, the slenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 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
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Table B2: Revised Criteria for Response Assessment (Continued)

Response and site	PET-CT based response	CT-based response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, 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-avid foci	New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; 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 deescalation is investigated, it may be preferable to consider a score of 3 as inadequate responses (to avoid undertreatment).
Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. 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 (eg, liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured 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 (eg, GI tract, liver, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

[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.

Source: Cheson, 2014

Appendix C: Guidelines for the Diagnosis and Treatment Response of Chronic Lymphocytic Leukemia: International Workshop on Chronic Lymphocytic Leukemia

The guidelines for the diagnosis and treatment response of chronic lymphocytic leukemia are outlined in a report by the International Workshop on Chronic Lymphocytic Leukemia Hallek, 2008) with modifications (Hallek, 2012; Hallek, 2013).

Table C1: Diagnostic Assessment of Chronic Lymphocytic Leukemia

Diagnostic Test	General Practice	Clinical Trial
History, Physical Examination	Always	Always
CBC and Differential Count	Always	Always
Marrow Aspirate and Biopsy	At cytopenia of uncertain cause	At CR or cytopenia of uncertain cause
Assessment for Minimal Residual Disease	Not generally indicated	Desirable
Ultrasound of the Abdomen	Possible, if previously abnormal	Not generally indicated
CT Scans of the Chest, Pelvis, and Abdomen	Not generally indicated	Recommended if previously abnormal and otherwise with a CR/PR

Abbreviations: CBC = complete blood counts; CR = complete response; CT = computerized tomography; PR = partial response.
Source: Hallek, 2008.

Table C2: Response Definition after Treatment for Chronic Lymphocytic Leukemia Patients

	Parameter	Complete Response	Partial Response	Partial Response with Lymphocytosis	Progressive Disease
Group A	Lymphadenopathy	None > 1.5 cm	Decrease ≥ 50%, no increase or new	Decrease ≥ 50%, no increase or new	Increase ≥ 50% or new (>1.5 cm)
	Hepatomegaly	None	Decrease ≥ 50% from baseline	Decrease ≥ 50% from baseline	Increase ≥ 50% or new
	Splenomegaly	None	Decrease ≥ 50% from baseline	Decrease ≥ 50% from baseline	Increase ≥ 50% or new
	Blood Lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Persistent lymphocytosis due to mechanism of action of IP	Increase ≥ 50% over baseline
	Marrow	Normocellular, < 30% lymphocytes, no B-lymphoid nodules Hypocellular marrow defines CRi	50% reduction in marrow infiltrate, or B-lymphoid nodules	50% reduction in marrow infiltrate, or B-lymphoid nodules	-
Group B	Platelet count	> 100,000/µL	> 100,000/µL or increase ≥ 50% over baseline	> 100,000/µL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
	Hemoglobin	> 11.0 g/dL	> 11.0 g/dL or increase ≥ 50% over baseline	> 11.0 g/dL or increase ≥ 50% over baseline	Decrease of > 2g/dL from baseline secondary to CLL
	Neutrophils	> 1500/µL	> 1500/µL or increase ≥ 50% over baseline	> 1500/µL or increase ≥ 50% over baseline	-

Complete Response (CR) = all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms;
CR with Incomplete Bone Recovery (CRi) = fulfills all criteria for a CR (including normal bone marrow biopsy and aspirate with no evidence of clonal infiltrate) except for persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to chronic lymphocytic leukemia (CLL) but likely related to drug toxicity;
Nodular PR (nPR) = persistent bone marrow nodules (immunohistochemistry has to determine if primariliy of T cells or lymphocytes other than CLL cells or CLL cells) on bone marrow biopsy in subjects achieving a CR; If bone amrrow is hypocellular then a repeat determination should be performed after 4 weeks.
Partial Response (PR) and Partial Response with Lymphocytosis (PRL) = at least two of the criteria of Group A plus one of the criteria of Group B have to be met for a minimum duration of 2 months; Stable Disease (SD) = is the absence of Progressive Disease (PD) and failure to achieve at least PR;
PD = at least one of the above criteria of Group A or Group B has to be met.
Source: Hallek, 2008.

Appendix D: Cairo-Bishop Definitions of Tumor Lysis Syndrome

Table D1: Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Laboratory Parameter	Laboratory Result
Uric Acid	≥ 476 µmol/L (≥ 8.0 mg/dL) or 25% increase from baseline
Potassium	≥ 6.0 mmol/L (≥ 6.0 mEq/L) or 25% increase from baseline
Phosphorous	≥1.45 mmol/L (≥ 4.5 mg/dL) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/L (≤ 7.0 mg/dL) or 25% decrease from baseline

Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).

Table D2: Cairo-Bishop Definition of Clinical TLS

The presence of laboratory TLS and one or more of the following criteria:
1. Creatinine: ≥ 1.5 ULN (age > 12 years or age adjusted)
2. Cardiac arrhythmia / sudden death
3. Seizure[a]

ULN = upper limit of normal.
[a] Not directly attributable to a therapeutic agent.

Table D3: Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrythmia	Seizure
0	-	≤ 1.5 × ULN	None	None
1	+	1.5 × ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 × ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 × ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 × ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death[a]	Death[a]	Death[a]

Abbreviations: ADL= activities of daily living; LTLS = laboratory tumor lysis syndrome; TLS= tymor lysis syndrome; ULN = upper limit of normal.
[a] Probably or definitely attributable to clinical TLS.
Source: Cairo, 2004

Appendix E: Grading Scale for Hematologic Toxicity in Chronic Lymphocytic Leukemia Studies

Grade[a]	Decrease in Platelets[b] or Hgb[c] (nadir) From Pretreatment Value (%)	Absolute Neutrophil Count[d] (mm^3) (nadir)
0	No change to 10%	≥ 2,000
1	11% - 24%	≥ 1500 and < 2000
2	25% - 49%	≥ 1000 and < 1500
3	50% - 74%	≥ 500 and < 1000
4	≥ 75%	< 500

[a] Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as Grade 5.

[b] Platelet counts must be below normal levels for Grades 1-4. If, at any level of decrease the platelet count is < 20,000/mm^3, this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20,000/ mm^3) was present pretreatment, in which case the subject is not evaluable for toxicity referable to platelet counts.

[c] Hemoglobin (Hgb) levels must be below normal levels for Grades 1-4. Baseline and subsequent Hgb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.

[d] If the absolute neutrophil count (ANC) reaches less than 1000/ mm^3, it should be judged to be Grade 3 toxicity. Other decreases in white blood cell count, or in circulating granulocytes, are not to be considered, since a decrease in white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in chronic lymphocytic leukemia for stepwise grading of toxicity. The use of granulocyte-colony-stimulating factor (G-CSF) is irrelevant for the grading toxicity, but should be documented.

Source: Hallek, 2008.

Appendix F: Lenalidomide Pregnancy Prevention Risk Management Plan

The Pregnancy Prevention Risk Management Plan is a standalone document.

Appendix G: Inhibitors or Inducers of CYP3A

Inhibitors and inducers of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 8.2 on instructions for concomitant use of CYP3A inhibitors or inducers with ibrutinib.

Inhibitors of CYP3A4/5	**Inducers of CYP3A4/5**
Strong inhibitors:	Carbamazepine
Indinavir	Efavirenz
Nelfinavir	Nevirapine
Ritonavir	Barbiturates
Clarithromycin	Glucocorticoids
Itraconazole	Modafinil
Ketoconazole	Oxcarbarzepine
Nefazodone	Phenobarbital
Saquinavir	Phenytoin
Telithromycin	Pioglitazone
Moderate inhibitors:	Rifabutin
Aprepitant	Rifampin
Erythromycin	St. John's Wort
Diltiazem	Troglitazone
Fluconazole	
Grapefruit Juice	
Seville Orange Juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
All Other Inhibitors:	
Amiodarone	
NOT Azithromycin	
Chloramphenicol	
Boceprevir	
Delaviridine	
Diethyl-Dithiocarbamate	

Inhibitors of CYP3A4/5	Inducers of CYP3A4/5
Fluvoxamine	
Gestodene	
iImatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
Star fruit	
Telaprevir	
Troleandomycin	

Abbreviation: CYP = cytochrome P450.
Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Appendix H: Criteria for Initiating Treatment in Subjects with CLL (Adopted and Modified from the IWCLL Guidelines for CLL Section 4)

Active disease should be clearly documented for protocol therapy. At least one of the following criteria should be met:

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia;
2. Massive (ie, at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly;
3. Massive nodes (ie, at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy;
4. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than 30×10^9/L (30 000/μL), LDT should not be used as a single parameter to define a treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded.
5. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy (see the IWCLL Guidelines for CLL section 10.2)
6. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
    a. Unintentional weight loss of 10% or more within the previous 6 months;
    b. Significant fatigue (ie, ECOG PS 2 or worse; inability to work or perform usual activities);
    c. Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or
    d. night sweats for more than 1 month without evidence of infection.

Hypogammaglobulinemia or monoclonal or oligoclonal paraproteinemia does not by itself constitute a basis for initiating therapy. However, it is recommended to assess the change of these protein abnormalities if patients are treated. Patients with CLL may present with a markedly elevated leukocyte count; however, the symptoms associated with leukocyte aggregates that develop in patients with acute leukemia rarely occur in patients with CLL. Therefore, the absolute lymphocyte count should not be used as the sole indicator for treatment.

7. Patients who have resistant disease, a short time to progression after the first treatment, and/or leukemia cells with del(17p) often do not respond to standard chemotherapy and have a relatively short survival. Therefore, such patients should be offered investigative clinical protocols, including allogeneic hematopoietic stem cell transplantation.

Source: Hallek, 2008.

Appendix I: Modified Cumulative Illness Rating Scale (CIRS)

RATING SUGGESTIONS (GENERAL PRINCIPLES)

Every single disease must be classified in the appropriate system. If there are several problems in the same system, only the most severe is rated. Example: For a patient suffering from a well-controlled angina (Rated 2) and terminal heart failure (Rated 4), only the higher rated condition would be scored in the Cardiac system (eg, rating is 4).

The spread of a cancer may lead to rating the condition in more than one category. For example, a lung cancer with bone metastases treated with nonsteroidal anti-inflammatory drugs (NSAID) is Rated 4 in Respiratory and 2 in Musculoskeletal.

General rules for severity rating:

0 - No problem affecting that system or past problem without clinical relevance.

1 - Current mild problem or past significant problem.

2 - Moderate disability or morbidity and/or requires first line therapy.

3 - Severe problem and/or constant and significant disability and/or hard to control chronic problems (complex therapeutic regimen).

4 - Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.

LEVEL 0

No problem or healed minor injuries; past childhood illnesses (chickenpox); minor surgery (carpal tunnel completely healed, caesarean); uncomplicated healed fractures; other past problems healed without sequel, residual or complication (pneumonia).

LEVEL 1

Any current medical problem that causes mild discomfort or disability, or has occasional exacerbations, having only minor impact on morbidity (asthma controlled with PRN ["as needed"] bronchodilators, occasional heartburn relieved with PRN antiacids). Medical problems that are not currently active but were significant problems in the past (passage of a kidney stone) or required major surgery (hysterectomy, cholecystectomy, appendectomy).

LEVEL 2

Medical conditions that require daily treatment or first line therapy (asthma controlled with inhaled steroids, gastro-esophageal reflux treated with daily medication, osteoarthritis requiring daily NSAID, etc.) and/or have moderate disability or morbidity.

LEVEL 3

Chronic conditions that are not controlled with first line therapy (asthma needing continuous corticosteroid therapy, symptomatic angina despite medical regimes, heart failure with symptoms or uncontrolled hypertension despite complex therapeutic regimen) and/or constant significant disability, but not severe disability.

LEVEL 4

Any acute condition that requires immediate treatment or hospitalization (unstable angina, acute myocardial infarction, stroke, but also bladder outlet obstruction) and/or extremely severe problems; organ failure (end-stage renal disease needing dialysis, oxygen-dependent chronic obstructive pulmonary disease, terminal heart failure); severe sensory impairment (almost complete blindness or deafness, being wheelchair bound) and/or severely affected quality of life, severe impairment in function; delirium by medical (organic) conditions.

RATING MALIGNANCIES

Consistent scoring of severity ratings for various malignancies is a difficult problem. Each malignancy has its own rating system and prognostic indicators, the complexity of which would quickly exceed the aim of the intended simplicity and ease of use of CIRS.

The following general guidelines are intended to provide a reasonably accurate delineation of medical burden for cancer without excessive complexity.

Level 1: Cancer diagnosed in the remote past without evidence of recurrence or sequel in the past 10 years or skin cancer excised in the past without major sequel (other than melanoma).

Level 2: No evidence of recurrence or sequel in the past 5 years.

Level 3: Required chemotherapy, radiation, hormonal therapy or surgical procedure for cancer in the past 5 years.

Level 4: Recurrent malignancy or metastasis (other than to lymph glands) or palliative treatment stage.

These ratings are to be made in the appropriate organ category for a given malignancy.

ORGAN-SPECIFIC CATEGORIES

The following organ specific categories will attempt to provide guidelines for consistent rating of comparable severity. Common conditions will be stressed with the focus on the "judgment strategy" that can be applied to other problems not listed.

If there are several conditions in the same system, only the most severe is rated.

HEART

In this category only heart and coronary diseases have to be considered (not vascular): coronary arteries disease, heart failure, valvular heart diseases, heart disease secondary to hypertension, endocardities, miocardities, pericardities, arrhythmias (extrasystoles, bundle-branch blocks, atrial fibrillation, pacemaker placement), heart malignancies. Functional impact must be considered too, eg, New York Hearth Association (NYHA) II heart failure has different value between dependent and independent persons.

0 - No problems

1 - Remote MI (> 5 years ago); occasional [exertion] angina; asymptomatic valvular disease

2 - Congestive heart failure (CHF) compensated with medications (NYHA I-II); daily anti-angina medications; left ventricular hypertrophy; atrial fibrillation, bundle branch block, daily anti-arrhythmic drugs (even for prophylaxis); pacemaker placement for

asymptomatic bradycardia (relieved by Holter electrocardiogram [ECG] monitoring); valvular disease requiring medical treatment

3 - Previous myocardial infarction (MI) (<5 years ago); abnormal stress test; status post (previous) percutaneous coronary angioplasty, coronary artery bypass graft surgery or other cardiac surgery (valve replacement); moderate CHF (NYHA II-III) or complex medical treatment; bifascicular block; pacemaker placement for cardiogenic syncope; pericardial effusion or pericarditis

4 - Acute coronary syndrome, unstable angina or acute MI; intractable CHF (NYHA III-IV acute or chronic); marked restriction to the normal activity of daily living secondary to cardiac status

HYPERTENSION

Consider only hypertension severity; organ damage (complications) should be considered into the respective categories.

0 - Normotension

1 - Borderline hypertension; hypertension compensated with salt restriction and weight loss, drug free (when drug therapy is indicated, but the patient does not take medications, the score is at least 2)

2 - Daily antihypertensive medications: hypertension controlled by 1 pill therapy (even fixed dose combinations)

3 - Hypertension requiring two or more pills for control

4 - Malignant hypertension, or hypertension not controlled by a complex therapeutic regimen

VASCULAR-HEMATOPOIETIC

Artery disease: carotid atherosclerosis, peripheral arteries disease (PAD), aneurysms (every site)

Venous disease: venous insufficiency, varices, deep venous thrombosis (DVT), pulmonary embolism, primary pulmonary hypertension

Hematopoietic disease: anemia, leucopenia, thrombocytopenia, hematological malignancy

Lymphopoietic disease: chronic lymphatic edema, lymphoma, spleen and thymus disease

Immunologic disease: systemic lupus erythematosus, systemic sclerosis (scleroderma), sarcoidosis, hypersensitivity

0 - No problem

1 - Venous insufficiency, varices, lymphedema; carotid stenosis <70%; hemoglobin 10-12 g/dl (in females), 12-14 g/dl (in males); anemia of chronic “inflammatory” disease

2 - Previous DVT; one symptom of atherosclerosis disease (claudication, bruit, amaurosis fugax, absent pedal pulses) or daily medications (eg, anti-platelets drugs); PAD IIa-IIb by Fontaine; carotid stenosis > 70%; aortic aneurysm < 4 cm; hemoglobin 8-10 g/dl (in females), 10-12 g/dl (in males); anemia secondary to iron, B12 vitamin or folate deficiency, or to chronic renal failure; total white blood cell (WBC) 2000-4000/mmc; mild thrombocytopenia (50000-150000/mmc)

3 - DVT or recent DVT (< 6 months ago); two or more symptoms of atherosclerosis (see above); PAD Fontaine III or recent/previous angioplasty (with or without stenting); hemoglobin < 8g/dl (in females), < 10 g/dl (in males); dyserythropoietic anemia; WBC < 2000/mmc; severe thrombocytopenia (< 50000/mmc)

4 - Pulmonary embolism (acute or recent/previous); atherosclerosis requiring surgical intervention (eg, aortic aneurysm > 4 cm, symptomatic carotid stenosis > 70%, PAD Fontaine IV or amputation for vascular causes, etc.); recent/previous vascular surgery; any hematological or vascular malignancy (including multiple myeloma)

In case of immunological disease, score should be assigned by considering blood abnormalities, stadium of organ damage and/or functional disability (2: symptoms controlled by daily medications; 3: symptoms not well controlled; 4: symptoms impossible to be controlled or short time poor prognosis)

RESPIRATORY

In this category, consider chronic obstructive pulmonary disease (COPD), asthma, emphysema, restrictive pulmonary interstitial lung diseases, malignancies of lung and pleura, pneumonia, and smoking status.

0 - No problem

1 - Recurrent episodes of acute bronchitis; currently treated asthma with PRN inhalers when required; cigarette smoker > 10 but < 20 pack years

2 - Instrumental diagnosis of COPD or pulmonary interstitial disease (x-ray, TC, spirometry); daily Prn inhalers (≤ 2 pharmacological classes); two or more episodes of pneumonia in the last 5 years; cigarette smoker < 20 but < 40 pack years

3 - Exertion dyspnea secondary to limited respiratory capacity, not well controlled by daily medications; required oral steroids for lung disease; daily PRN inhalers (3 pharmacological classes); acute pneumonia treated as an outpatient

4 - Chronic supplementation of oxygen; respiratory failure requiring assisted ventilation, or previous (at least one episode); any lung or pleural neoplasm; acute pneumonia requiring hospitalization

Smoking is an important respiratory and cardiovascular risk, so it is considered as a disease, and it is rated according to *lifetime pack years*:

Number of cigarette packs smoked per day × Number of years smoked in their lifetime

eg, 1 pack year = 20 cigarettes/day (1 pack) × 1 year

Ex-smokers should be rated too, but those who have been smoke free for the most recent 20 years would merit a lower rating than currently smoking

Examples:

A. Patient smoking 20 cig/day (1 pack) for 25 years = 25 pack years – CIRS score: 2

B. Patient smoking 40 cig/day (2 packs) for 25 years = 50 pack years – CIRS score: 3

C. Ex-smoker of 20 cig/day (1 pack) for 25 years, he stopped 5 years ago – CIRS score: 2

D. Ex smoker of 20 cig/day (1 pack) for 25 years, he stopped 20 years ago – CIRS score: 1

Classification of COPD could be more specific when instrumental data (objective evidence) are available: blood gases, forced expiratory volume in 1 second (FEV1), etc.

EYES, EARS, NOSE & THROAT, and LARYNX

To simplify the potential complexity of this category it was decided to score according to the severity of the disability created by sensory diseases (degree of limited autonomy and communication), and avoid rating each type of pathology. Sensory impairments should be rated **after** instrumental correction (corrective lenses, hearing aid, etc.).

Eyes: glaucoma, cataracts, macular degeneration (diabetic/hypertensive retinopathy), any other pathology

Ears: otitis, dizziness, any cause of hearing impairment

Nose & Throat: rhinitis, pharyngitis, nasal polyps, sinusitis, malignancies

Larynx: dysphonia, acute and chronic laryngitis, malignancies

0 - No problems

1 - Corrected vision with glasses; mild hearing loss; chronic sinusitis

2 - Difficulty in reading newspaper or drive although glasses; required hearing aid; chronic sinonasal complaints requiring medication; vertigo/dizziness requiring daily medications

3 - Severe low vision, partially blind (required an escort to venture out, unable to read newspaper); severe ear impairment (conversational heading still impaired with hearing aid); laryngeal dysphonia (not neurological dysarthria)

4 - Functional blindness/deafness: unable to read, recognize a familiar face, unable to conversational heading, even if "organically" he is not completely blind or deaf; laryngectomy (every cause, especially malignancies); required surgical intervention for vertigo; aphonia secondary to laryngeal impairment.

UPPER GASTROINTESTINAL SYSTEM

This category is comprehensive of the intestinal tract from esophagus to duodenum, and pancreatic trees: dysphagia, gastroesophageal reflux disease (GERD), hiatal hernia, esophageal diverticula, any type of gastritis (consider also H. Pylori eradication or not), gastric/duodenal ulcer, acute or chronic pancreatitis, malignancies (comprehensive of gastric lymphoma).

Pay attention that type 1 diabetes is rated under "metabolic."

0 - No problem

1 - Hiatal hernia, GERD or gastritis requiring PRN medications; previous ulcer (> 5 years ago); previous Helicobacter pylori eradication therapy (> 5 years ago)

2 - Daily proton pump inhibitor/anti-acid medications; documented gastric or duodenal ulcer or Helicobacter pylori eradication therapy within 5 years

3 - Active gastric or duodenal ulcer; positive fecal occult blood test; any swallowing disorder or dysphagia; chronic pancreatitis requiring supplemental pancreatic enzymes for digestion; previous episode of acute pancreatitis

4 - Any type of malignancies (see "Rating Malignancies"); previous gastric surgery because of cancer; history of perforated ulcer (gastric surgery not because of cancer, ulcorrhaphy); melena/heavy bleeding from upper gastrointestinal (GI) source; acute pancreatitis

LOWER GASTROINTESTINAL SYSTEM

Comprehensive of the rest of the GI system, from small bowel to anus: Whipple's disease, diverticulosis, irritable bowel, malignancies. Constipation is rated, too, by type and frequency of laxatives required, or by history of impaction.

0 - No problems, previous appendectomy, previous hernia repair (without complications)

1 - Constipation managed with PRN medications; active hemorrhoids; intestinal hernia requiring surgery; previous hernia repair with complications (intestinal adherences, laparocele, etc.); irritable bowel syndrome (few symptoms)

2 - Constipation requiring daily bulk laxatives (psyllium, policarbophil, sterculia, guar gum, etc.), or stool softeners; diverticulosis (previous diverticulitis); inflammatory bowel disease in remission with medications (> 5 years ago)

3 - Bowel impaction/diverticulitis within the last year; daily use of stimulant (irritant) or osmotic laxatives (bysacodil, senna, glycerol, sodium docusate; lactulose, polyethylene glycol) or enemas; chronic bowel inflammation in remission with medications (<5 years ago)

4 - Diverticulitis flare up; active inflammatory disease; current impaction; hematochezia/active bleeding from lower GI source; bowel carcinoma

LIVER AND BILIARY TREES

Comprehensive of liver, gallbladder, biliary trees, portal system: acute and chronic hepatitis (viral, alcoholic, toxic, autoimmune, idiopathic), cirrhosis, portal hypertension, hemochromatosis, primary biliary cirrhosis, cholelithiasis, cholangitis, primary malignancies. As the hepato-biliary system is difficult to assess through the physical examination, therefore, laboratory results must be used.

0 - No problem

1 - History of hepatitis (actually normal values of transaminases); cholecystectomy

2 - Cholelithiasis; chronic hepatitis or previous hepatitis (<5 years ago) or any other liver disease (hemochromatosis, primary biliary cirrhosis) with mildly elevated transaminases (within 3-times normal values); heavy alcohol use within 5 years (should be rated in "psychiatric" category also)

3 - Chronic hepatitis or any other liver disease with marked elevation of transaminases (>3-times normal values); elevated bilirubin

4 - Acute cholecystitis; any biliary obstruction; active hepatitis/liver cirrhosis; any liver or biliary tree carcinoma

RENAL

This category is exclusive of kidney: kidney stones, acute/chronic renal failure, glomerulonephritis; nephrosic/nephritic syndrome; active/chronic pyelonephritis, diabetic or hypertensive nephropathy (albuminuria/proteinuria), renal carcinoma.

Bence-Jones proteinuria in multiple myeloma should not be considered.

0 - No problem exists

1 - Asymptomatic kidney stone; kidney stone passage within the last ten years; pyelonephritis within 5 years; kidney cysts without hematuria

2 - Serum creatinine > 1.5 but < 3 mg/dl without diuretic or antihypertensive medication (particularly angiotension converting enzyme-inhibitors or systemic renin-angiotension-aldesterone blockers); kidney calculi requiring daily medications

3 - Serum creatinine > 3 mg/dl or > 1.5 mg/dl in conjunction with diuretics, antihypertensive, or bicarbonate therapy; active pyelonephritis; nephrosic syndrome; colic symptoms treated as an outpatient

4 - Required dialysis; renal carcinoma; colic symptoms requiring hospitalization

GENITOURINARY

Ureters, bladder, urethra.

Genitals, prostate, testicles, penis, seminal vesicles.

Uterus, ovaries. *Mammary gland is rated under "metabolic."*

This category is comprehensive of all genitourinary tract impairments: ureteral or bladder stones, benign prostate hypertrophy (BPH), urinary tract infections (UTIs), prolapses, etc. Urinary incontinence and indwelling catheter should also be considered.

0 - No problem

1 - Stress incontinence; BPH without urinary symptoms; hysterectomy or ovariectomy (uterine fibroma, benign neoplasm)

2 - Pathological pap smear (or 2 consecutives abnormal); frequent UTIs (3 or more in the past year) in female or current UTIs; urinary incontinence (not stress) in females; BPH with urinary symptoms (frequency, urgency, hesitancy); status post transurethral resection of the prostate (TURP); any urinary diversion procedure; indwelling catheter; bladder calculi

3 - Prostatic cancer in situ (eg, incidentally found during TURP); vaginal bleeding; cervical carcinoma in situ; hematuria (any cause); urinary incontinence (not stress) in males; bladder polyps

4 - Acute urinary retention; current urosepsis; any genitourinary malignancies except as above

MUSCULOSKELETAL/INTEGUMENT

This is a very wide category, including: osteoarthritis, osteoporosis, any bone fracture; primary neoplasm (bone, muscle, connective tissue, skin), distinguishing melanoma from other localized

skin cancers; rheumatoid arthritis and polymyalgia rheumatica; muscular injuries (rotator cuff, long head of the biceps); pressure sores; any dermatological disease.

The scores of this category are strictly correlated to the disability they cause; for the evaluation of the level of disability, refer to basic activities of daily living and instrumental activities of daily living

NOTICE: Score the severity of each illness according to the level of disability caused by the same illness in this category, without considering the disability caused by other diseases. For example: A patient affected both by osteoarthritis and hemiplegia from a previous stroke has a high level of disabilityand must be scored 2 for disability by osteoarthritis (in this category) and 4 for disability by stroke (in the neurological category); for a patient with both a deforming rheumatoid arthritis and a previous stroke without remaining outcomes, score 4 for disability from arthritis (in this category) and 2 for disability from stroke (in the neurological category).

0 - No problem exists

1 - Requires PRN medications for osteoarthritis (NSAID) or has mildly limited IADL from joint pathology; excised skin cancers (except melanoma); skin infections requiring antibiotics within a year

2 - Daily anti-osteoarthritis medications (NSAID) or use of assisitive devices or little limitation in ADL (previous arthroprosthesis or treated fracture with a low level of remaining disability); osteoporosis without vertebral fractures; daily medications for chronic skin diseases (even local, as psoriasis or pressure sores); non metastatic melanoma; daily medications for rheumatoid arthritis (except steroids) with a low level of disability

3 - Osteoarthritis with a moderate level of disability in ADL; requires chronic treatment with steroids for arthritic conditions or joints' deformities or severely impaired; osteoporosis with vertebral compression fractures

4 - Wheelchair bound for osteomuscular disease; severe joint deformities or severely impaired usage; osteomyelitis; any bone or muscle or connective tissue neoplasm (see "Rating Malignancies"); metastatic melanoma.

Fractures and/or arthroprosthesis (both recent and old) have to be scored according to the level of disability they cause (considering outcomes also), in order to avoid confusion about possible classifications of different fractures or joints. The same for muscular diseases.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

This category includes the "somatic" pathologies of the central and peripheral nervous system: any kind of stroke, neurodegenerative diseases (Parkinson's disease and parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis, etc.), myelopathies, traumas with neurological outcomes, primary or secondary epilepsy, neuropathies (diabetic, alcoholic, any other etiology), primary tumors, chronic headaches (migraine), insomnia, etc. It must carefully estimate the severity and prognosis of the illness but also the functional impairment that the illness causes.

0 - No problem (or fewer convulsions in childhood)

1 - Frequent headaches requiring PRN medications without impairment in Advanced ADL; previous transient ischemic attack (TIA) (one event); previous epilepsy, actually not treated, without crisis since more than 10 years ago.

2 - Chronic headache requiring daily medications (even for prophylaxis) or with regularly functional impairment in Advanced ADL (bed rest, job withdrawal, etc.); actual TIA or more than one previous TIA; previous stroke without significant residual; mild severity neurodegenerative diseases (see above), treated and well controlled; epilepsy controlled with drugs.

3 - Previous stroke with mild residual dysfunction (hemiparesis, dysarthria); any neurosurgical procedure; moderate severity neurodegenerative diseases (see above), not well controlled by medications; epilepsy in treatment but with periodic crisis.

4 - Acute stroke or previous stroke with severe residual dysfunction (hemiplegia, aphasia, severe vascular dementia) or more than one previous stroke (multi-infarct encephalopathy); severe neurodegenerative diseases (see above) causing disability in ADL; neurological coma.

Alzheimer's disease and dementia should not be rated into this category (Psychiatric and behavioral diseases): Alzheimer's disease should be listed only under psychiatric disorders; if dementia stems from vascular and/or mixed dementia and/or other neurological condition (eg, Parkinson's Disease), both "neurologic" and "psychiatric" categories should be endorsed at the appropriate level for severity, considering in this category the stroke and the multi-infarct encephalopathy responsible for the cognitive impairment (score 3 for stroke with remaining outcomes, score 4 for multi-infarct encephalopathy).

ENDOCRINE-METABOLIC SYSTEM AND BREAST (including systemic infections and poisonings)

Type 1 and type 2 diabetes (organ damage should be considered into the respective categories, like for hypertension), obesity and dyslipidemia (hypercholesterolemia) represent the core of this category; it includes also hypo- and hyper-thyroidism, hypo- and hyper-parathyroidism, adrenal pathologies (Cushing' or Addison' disease), hypogonadism, hypopituitarism, etc. Malignancies of these glands, both benignant (like thyroid nodules) and malignant (like thyroid or adrenal cancer, vipoma, etc.) are also included.

Even if it is an exocrine gland, breast was included in this category because the authors could not find a more appropriate one; thus, it includes breast cancer also.

Moreover, it includes: electrolyte disorders, sepsis, systemic infections (like tuberculosis, syphilis, AIDS) scored according to their severity and the functional impairment they cause (see general indications) and poisonings (chronic by metals or acute by pesticides or carbon monoxide).

0 - No problem

1 - Diabetes and/or dyslipidemia compensated with diet; mild obesity (Body mass index [BMI] 30 -35 kg/m2); hypothyroidism in replacement therapy (L-thyroxin); hyperthyroidism caused by Plummer' adenoma surgically treated.

2 - Diabetes compensated with oral hypoglycemic drugs or insulin (hemoglobin A1c < 7%); dyslipidemia well controlled by daily medications (low density lipoprotein cholesterol [c-LDL] lower than the recommended target according to the individual global cardiovascular risk); moderate obesity (BMI 35-45 kg/m2); hyperthyroidism (Basedow, Plummer) in pharmacologic treatment; asymptomatic or surgically treated hyperparathyroidism; fibrocystic breast disease.

3 - Diabetes not well compensated by therapy (hemoglobin A1c 7-8.5%, presence of complications); dyslipidemia not well controlled (c-LDL higher than the recommended target according to the individual global cardiovascular risk; for instance, c-LDL> 100 mg/dl in patients with previous myocardial infarction or stroke); severe obesity (BMI > 45 kg/m2); symptomatic hyperparathyroidism (for instance, hypercalcaemia); replacement therapy for adrenal failure; any electrolytes disorder requiring hospitalization.

4 - Uncontrolled diabetes (hemoglobin A1c > 8.5%) or one diabetic ketoacidosis or nonketotic hyperosmolar coma during the past year; genetic uncontrolled dyslipidemia; acute adrenal failure during hormonal replacement therapy; any neoplasm of thyroid, breast, adrenal gland (see "Rating Malignancies").

NOTICE: When the patient is not treated with drug therapy for diabetes or dyslipidemia but he should be for the optimal control of the pathology (for instance, hemoglobin A1c > 7%, total cholesterol > 250 mg/dl), score the pathology according to the laboratory values, which really define its severity.

PSYCHIATRIC AND BEHAVIORAL DISEASES

This category includes both dementia and related behavioral disorders (psychosis, anxiety, depression, agitation) and all the pre-existing and/or not related to dementia psychiatric disorders. Since this is the only item analyzing patient's mental status (all the others refer to physical status), it is very important to evaluate it considering carefully further information derived from the Comprehensive Geriatric Assessment (MMSE; Geriatric Depression Scale [GDS], Neuro-Psychiatric Inventory if available).

0 - No psychiatric problem or history thereof

1 - Minor psychiatric condition or history thereof: previous (occasional) psychiatric treatment without hospitalization; major depressive event and/or use of antidepressants more than 10 years ago without hospitalization; occasional use of minor tranquilizers (eg, benzodiazepins; even if as hypnotherapy for insomnia); mild cognitive impairment (MMSE 25-28).

2 - A history of major depression (according to DSM-IV [Diagnostic and Statistical Manual of Mental Disorders-IV] criteria) within the last 10 years (treated or untreated); mild dementia (MMSE 20-25); previous admission to Psychiatric Department for any reason; history of substance abuse (more than ten years ago, including alcoholism).

3 - Current major depression (according to DSM-IV criteria) or more than two previous major depression episodes in the past 10 years; moderate dementia (MMSE 15-20); current and usual usage of daily anti-anxiety medications (even as hypnotherapy for

insomnia); current or within the past ten years substance abuse or dependence (according to DSM-IV criteria); requires daily antipsychotic medication; previous attempt at suicide.

4 - Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management (psychiatric emergency, as attempt at suicide or severe depression with suicide purpose, acute psychosis or acute decompensation of chronic psychosis, severe substance abuse; severe agitation from dementia); severe dementia (MMSE < 15); delirium (acute confusion or altered mental status for medical (organic) reasons: in this case, codify also the medical cause in its own category with the appropriate level of severity).

It could be requested psychiatric consult for this category; dementia and depression, the most frequent diseases in the elderly, can be scored in details using the MMSE and GDS. The severity of any mental disorder (dementia, depression, anxiety, psychosis, substance abuse and all the others) has to be scored according to the level of functional impairment or disability they cause.

Source: Salvi, 2008b

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Tuesday, 26 May 2020, 04:06 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

The purpose of Protocol Amendment #4 is twofold.

First, to address a formulation change for ibrutinib study treatment. Currently supplied as 140 mg capsules, this formulation is no longer commercially available. The new formulation is a 140 mg tablet with the same active ingredient. The tablets were commercially approved as being equivalent to the original formulation.

The second purpose of this amendment is to allow subjects to be followed as per standard of care according to the investigator's medical judgement.

At the time of this Protocol Amendment #4, 10 subjects are receiving ibrutinib monotherapy.

Significant changes included in this amendment are summarized below:

- **Subjects will move to a tablet formulation when the capsule formulation is no longer commercially available.**

Commercially sourced 140 mg capsule formulation is being substituted on the markets by a 140mg tablet formulation.

Tablets will be supplied in a blister pack instead of a bottle. Ibrutinib administration was updated to note the study treatment will be supplied as either capsules or tablets.

Revised Sections: Section 7.1.4, Section 7.7, and Section 7.2.1.2.2

- **For subjects continuing on ibrutinib, scheduled clinic visits will be done according to standard of care per investigator's discretion**

Subjects on ibrutinib are routinely followed every three months as standard of care, not the current monthly schedule. The schedule for investigational product (IP) dispensing and treatment visits will be done per the investigator's medical judgement and standard of care at the investigative site.

The investigator remains responsible to monitor safety, record adverse events (AEs)/serious adverse events (SAEs)/second primary malignancies(SPMs) in source documents, and report SAEs and SPMs to Celgene Drug Safety.

Revised Sections: Protocol Summary, Section 3.2.3, Section 5/Table 8, Section 6.2, Section 6.3.2, and Section 6.5.

1. JUSTIFICATION FOR AMENDMENT

The purpose of Protocol Amendment 3 is to close the study, discontinue the Follow-up Period, and stop data collection in the clinical database.

Following completion or discontinuation of durvalumab therapy per protocol for all subjects (n=106), and completion of the primary analysis (data cutoff date 06 Mar 2019, defined as last durvalumab subject's 90-day Safety Follow-up Visit), there are no further plans to evaluate long-term efficacy, including overall survival for the remaining subjects on study. Therefore, the Follow-up Period will be discontinued, and data collection will stop under this amendment. No additional statistical analysis on safety and efficacy will be performed.

At the time of primary analysis data cutoff, 36 subjects were in follow-up. There were 13 subjects on ibrutinib treatment (Arm B), and no subjects on treatment with lenalidomide or bendamustine. Subjects receiving benefit from ibrutinib may continue to receive ibrutinib on-study per investigator's medical judgement or discontinue study to receive ibrutinib commercially as standard of care treatment (off-study).

Subjects who received lenalidomide will continue to be followed for second primary malignancies (SPMs) as required by [redacted] After stopping data collection in the clinical database, any SPM events will continue to be collected in the safety database.

Significant changes included in this amendment are summarized below:

- **Discontinuation of Follow-up Period, assessments and data collection**

Subjects who completed or discontinued durvalumab and all other study treatments, are no longer required to be followed for disease progression, subsequent antilymphoma/chronic lymphocytic leukemia (CLL) therapy, and overall survival. Follow-up procedures, efficacy assessments, central labs, imaging, and survival data can stop and will not be collected in the case report forms (CRFs).

Revised Sections: Protocol Summary, Section 3.2.3, Table 7, Table 8, Table 9, Table 10, Section 6.3.2, and Section 6.4.1.1.

- **Subjects on ibrutinib therapy (Arm B) and discontinuation of follow-up data collection**

In Arm B, ibrutinib continuous dosing is once daily until disease progression, unacceptable toxicity, starts new therapy, or discontinuation for any other reason, ie, subject withdraws consent or discontinues per investigator's discretion. Subjects may discontinue study to receive ibrutinib commercially as standard of care treatment (off-study).

Subjects receiving benefit from ibrutinib may continue ibrutinib on-study based on investigator's medical judgment. Follow-up efficacy assessments, central labs, imaging, and survival data will not be collected in the CRFs. The investigator remains responsible to monitor safety, record adverse events (AEs)/serious adverse events (SAEs) in source documents, and report SAEs to Celgene Drug Safety as stipulated under the full protocol.

Revised Sections: Protocol Summary, Section 3.2.2, Section 3.2.3, Section 6.2.1, Section 6.3.2, Section 6.4.1.1, Section 7.2.1.2, Section 10.1, and Section 10.5.

- **Second Primary Malignancies (SPMs) data collection**

Collection and monitoring of second primary malignancies will continue as events of interest and will be reported as SAEs regardless of treatment arm. For SAE reporting, SPMs are considered "Important Medical Events" if no other serious criteria apply. The SPM events will continue to be documented in the subject's source documents and reported as SAEs to Celgene Drug Safety. It is no longer required to collect SPMs in the clinical database, ie, AE and SPM CRFs.

Revised Sections: Protocol Summary and Section 10.7.1.

The amendment also includes several other minor clarifications:

- Editorial updates. – Protocol Summary, Table 3, Section 10.6 and Section 15.2.
- Revised length of study from 8 years to 6 years. – Protocol Summary and Section 3.2.
- Removed Canada and Health Canada. Protocol was not opened for enrollment in Canada. – Section 7.1.3, Section 7.1.4, Section 7.1.5, and Section 15.2.
- Clarification on ibrutinib's dose modifications and toxicity management will be per investigator's medical judgement. – Section 7.2.10.5 and Section 7.2.10.7.
- Updated the originally planned statistical analyses due to the enrollment stop, discontinuation of dose expansion cohorts, and discontinuation of the Follow-up Period. – Section 9.1, Section 9.2, Section 9.3, and Section 9.6.
- Specified that no additional analyses will be generated after the primary analysis data cutoff date (06 Mar 2019). Any data generated after this date will be maintained in the source documents and not required to be entered in the clinical database. – Section 9.8, Section 14.1, and Section 14.2.

1. JUSTIFICATION FOR AMENDMENT

Protocol Amendment 2 is written to update the Toxicity Management Guidelines (TMGs) and to reflect that on 05 Sep 2017 the United States (US) Food and Drug Administration (FDA) placed a Partial Clinical Hold on this study. 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.

Significant changes included in this amendment are summarized below:

- **Discontinuation of Arm A to the enrollment of new subjects**

Arm A (durvalumab plus lenalidomide with or without rituximab) is discontinued to the enrollment of new subjects. Only those subjects already enrolled and treated who are receiving clinical benefit, based on the discretion of the investigator, can remain on treatment after being informed and reconsented on the safety concerns with the combination of a programmed cell death-1 (PD-1) pathway inhibitor and an immunomodulatory agent. In addition, the add-on combination treatment with lenalidomide ± rituximab is no longer allowed. Other treatment arms in this study will continue unchanged.

Changes to the protocol have been made in the Protocol Summary and Sections 2 through 7 and 9 to reflect discontinuation of enrollment to Arm A.

- **Updates to the Toxicity Management Guidelines (TMGs)**

Update have been made to the general dose modification and TMGs (Tables 30, 31, and 32).

Other changes:

- Addition of approved durvalumab indication for the treatment of locally advanced or metastatic urothelial carcinoma (Section 1.2.1)
- Addition of rituximab intravenous biosimilars and rituximab subcutaneous usage for dose administration as they are becoming standard of care in some study sites (Section 7.1.3)
- Inclusion of risk of hepatitis B virus reactivation for ibrutinib as per ibrutinib summary of product characteristics (Section 8.3.1)
- Correction of typographical errors and updated tables and table footnotes consistently with the revised text throughout the document.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Addition of 2 new dose levels (ie, dose levels -2 and -3) to the Arm A dose finding part**

Initially, 4 potential dose levels were planned in Arm A. The doublet combination of durvalumab and lenalidomide 20 mg (dose level 1) was studied and deemed tolerable by the dedicated Safety Review Committee (SRC) as 0 of 3 subjects dosed was reported with a dose limiting toxicity (DLT) during Cycle 1. Thus, the triplet combination of durvalumab 1500 mg every 4 weeks (Q4W) and lenalidomide 20 mg plus rituximab (375 mg/m^2 weekly × 4 in Cycle 1 and then Day 1 of Cycles 2 through 5) (dose level 2) followed. This dose level was deemed not-tolerated by the SRC as 3 of 3 subjects dosed were reported with at least 1 DLT during Cycle 1. Consequently, the next 3 subjects were assigned to the subsequent lower dose level which is the same triplet combination with a reduced dose of lenalidomide 10 mg (dose level -1B). This dose level is currently being evaluated for DLTs.

In case dose level -1B is found to be not-tolerated by the SRC, new dose levels (ie, dose levels -2 and -3) are planned with the triplet regimen described in this protocol amendment. In dose levels -2 and -3, the combinations of durvalumab 1500 mg Q4W, lenalidomide 15 or 10 mg with rituximab at a less dose-intense schedule (ie, 375 mg/m^2 Q4W in Cycles 1 through 8) will be studied for tolerability.

For these new 2 dose levels, up to 12 additional DLT evaluable subjects may need to be treated to confirm a preliminary recommended Phase 2 dose (RP2D).

(Protocol Summary, Sections 3.1, 3.2.2, 4.1, 7.2.1.1, and 9.3.1.1, Figures 2 and 4, Tables 7 and 20)

- **Change to the allowed time windows for pretreatment archival lymph node/tumor biopsy and on treatment Cycle 2 biopsy samples, and removal of the requirement of a fresh frozen biopsy sample**

Effective development of novel targeted therapies depends on the identification of correlative biomarkers in an attempt to identify patients who are most likely to benefit from these agents. Experience with the use of durvalumab in patients with solid tumors showed that higher response rates were observed in subjects with programmed cell death ligand-1 (PD-L1)-positive tumors, compared with subjects with PD-L1 negative tumors in their pretreatment biopsy samples (Segal, 2014). Thus, further evaluation of these biomarkers and a broad exploration of additional biomarkers related to immunological and disease factors are needed to identify predictive biomarkers for durvalumab therapy in lymphoid malignancies.

As tumors may change their biologic profile over time and potentially in response to intervening treatments, an archival lymph node/tumor biopsy sample collected 18 months before study treatment start (as initially allowed) might not accurately reflect current molecular characteristic of tumor. To allow for an accurate assessment of tumor characteristics at baseline, an archival lymph node/tumor formalin fixed, paraffin embedded (FFPE) sample acquired by a surgical or core needle biopsy within 3 months prior to signing informed consent and with no intervening treatment after the biopsy is acceptable for enrollment of a subject with a poorly accessible tumor for biopsy following discussion with the sponsor's medical monitor.

Initially an on-treatment biopsy sample collection (strongly recommended) was planned at Cycle 2 Day 15 (± 3 days). The collection of this biopsy sample will be allowed at any time during Cycle 2 for greater logistical flexibility.

In addition, as the current technological advancements have made it possible to run the planned analyses on FFPE samples alone, a fresh frozen biopsy sample will not be necessary to submit for biomarker studies.

(Sections 3.2.1, 4.2, 6.1, and 6.2)

- **Removal of Aiolos/Ikaros analysis (Arm A)**

Aiolos and Ikaros are the downstream substrates of Cereblon which is the molecular target of lenalidomide and other immunomodulatory (IMiDs®) compounds. The analyses in other durvalumab studies suggest that durvalumab has no effect on degradation of those substrates when given in combination with an IMiD compound. Thus, the planned blood collections and analyses (ie, pre- and 5 hours post dose at Cycle 1 Day 1, and Cycle 2 Day 1 and Day 15) for Aiolos and Ikaros in Arm A were removed.

(Protocol Summary, Sections 1.3.6, 2, and 6.8.3 and Table 2)

- **Change to the secondary efficacy endpoints (Phase 1/2)**

Time to first response has been added as an additional secondary endpoint for further characterization of disease response. The timeframe for secondary overall response rate endpoint has been changed from 'during the study treatment' to 'during the study' which will be inclusive of any study treatment related response documented during the treatment and follow-up periods of the study as objective responses to immune checkpoint inhibitors can take considerably longer to become apparent compared with conventional therapies and continued disease regression can be reported well after completion of the treatment.

(Section 2 and Table 2)

- **Revision of inclusion criterion #6**

Inclusion criterion #6 which defines subjects with high-risk chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), will be changed to allow the inclusion of subjects who failed therapy on any Bruton's tyrosine kinase (BTK) inhibitor (not only ibrutinib). As clinical trials with other BTK inhibitors (eg, acalabrutinib, tirabrutinib) are currently ongoing, there is an emerging patient population who fail on these newer or experimental BTK inhibitors, and who are considered to meet the criteria of high-risk CLL/SLL, too.

(Section 4)

The amendment also includes several other updates, clarifications and corrections:

- Addition of the informal study name "FUSION NHL 001" to the title page. The study name was added to allow easier conversational identification for potential subjects and health care professionals. (Title Page and Protocol Summary)
- Addition of an exploratory objective and endpoint for assessment of abscopal effect (ie, immune-mediated tumor response outside the radiation field) with local IFRT when given in combination with durvalumab. (Protocol Summary, Table 1)

- Revision of the name of the treatment arms to accommodate a case in which a doublet regimen may be a recommended regimen for Phase 2 instead of a planned triplet regimen based on the emerging data. (Protocol Summary, Section 3.1 and 7.2, Table 3)
- Clarification that in the United States (US), treatment Arm D will enroll, pending availability of treatment slots, following the completion of response evaluation from the combination therapy arms (ie, Arms A, B, and C). (Protocol Summary, Section 3.1, and Figure 2)
- Update of the number of subjects planned for:
  - Arm A dose finding part: revision from "6 to 18" to "6 to 30" DLT evaluable subjects with the addition of 2 new potential dose levels (N = 12)
  - Arm C dose finding part: correction of the number of DLT evaluable subjects from "6 to 18" to "3 to 18"
  - Overall dose finding part: revision from "18 to 48" to "15 to 60" DLT evaluable subjects
  - Overall study: revision from approximately 253 to 265 subjects

  (Protocol Summary, Sections 3.1, 4.1, and 9, Table 3)
- Further description of the treatment assignment process as follows: "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." (Protocol Summary, Sections 3.1 and 3.2.2)
- Update with new indications which have been approved for lenalidomide and ibrutinib in the US and/or Europe. (Sections 1.2.2 and 1.2.3)
- Update with new indications which have been approved for the PD-1/PDL-1 blocking antibodies (ie, nivolumab, pembrolizumab, and atezolizumab) in the US, Europe, and/or Japan. (Section 1.3.1)
- Addition of Bendeka® as a reference product for bendamustine. (Sections 1.2.4 and 17)
- Update of the entire section to clarify objectives of the translational development plan, including the addition of recent studies which suggest additional evidence of the value of pretreatment tumor characteristics and certain microenvironment changes in on-treatment tumor samples which may provide both prognostic correlative biomarkers and predictive correlative biomarkers for response (Rizvi, 2015; Higgs, 2016). Addition of specific sampling for biomarker assessments for each arm to Table of Events. Addition of blood collection for biomarker peripheral blood mononuclear cell (PBMC) isolation at Cycle 2 Day 15 to allow comparison of biomarkers assessed in blood with on-treatment biopsies collected during Cycle 2. (Sections 1.3.6, 6.4.1.4 and 6.4.2.3, and Tables 7, 8, 9 and 10).

- Clarification that monitoring of minimal residual disease (MRD) will be performed in mantle cell lymphoma (MCL) and CLL by multi-color flow cytometry techniques and follicular lymphoma (FL) by polymerase chain reaction techniques. Removal of the MRD monitoring by next generation sequencing (NGS) technique. Split the MRD blood and bone marrow samples from the planned biomarker samples specified in Section 6.8. Addition of a whole blood sample at Cycle 1 Day 1 for baseline and repeat bone marrow aspirate samples (as available) along with peripheral blood for monitoring of the MRD. Elaborated the timing for submission of a bone marrow aspirate sample and/ or blood sample for monitoring of MRD. (Sections 1.3.6, 6.4.1.4, and 6.4.2.3, Tables 7, 8, 9 and 10)
- Further elaboration of exploratory pharmacodynamic and biomarker endpoints. (Protocol Summary and Table 2)
- Clarification that the MRD data will be reported in the clinical study report. (Table 1)
- Clarification that the SRC dedicated to each treatment arm can review and make recommendations for assessment of different dosing schedules based on the emerging study data as necessary. (Section 3.1)
- Clarification on the characteristics of pseudoprogression which have been noted with immune checkpoint inhibitors and referenced the "*Refinement of Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy*" for further guidance (Cheson, 2016). Clarification that subjects may continue receiving study treatment based on the investigator's discretion in situations where the investigator cannot determine true tumor progression. (Section 3.1.1)
- Clarification that the safety laboratory results must be reviewed by the investigator prior to first dose on Cycle 1 Day 1 to reconfirm subject eligibility with additional guidance on use of central and/or local laboratory results for dosing decisions consistent with Section 6. (Sections 3.2.2 and 6.2)
- Addition that subjects who receive local IFRT will follow the Arm D visit schedule and assessments and subjects who receive combination agents will follow the visit schedules and assessments specific to each combination regimen to be consistent with Section 6.2. (Section 3.1.2)
- Clarification in the overall study flow figure that the efficacy assessments will continue during the Follow-up Period until start of a new subsequent antilymphoma/CLL therapy, end of the Efficacy Follow-Up Period, or withdrawal of informed consent form in addition to first disease progression, whichever occurs earlier. (Section 3.2.3 and Figure 3)
- Clarification that subjects with DLBCL not otherwise specified or T-cell/histiocyte rich B-cell lymphoma histologies will be eligible for the DLBCL cohorts planned for the dose confirmation and expansion parts. (Table 3)
- Addition of abbreviations for each lymphoma histology (eg, cHL for classical Hodgkin lymphoma). (Tables 4 and 5)

- Revision of inclusion criterion 4 to list eligible and the exclusion criterion 2 to specify ineligible histologies consistently with Table 3, Table 4, and Table 5 for the dose confirmation and expansion parts of the study. (Sections 4.2 and 4.3)
- Clarification to inclusion criterion 9 that a previously irradiated lesion will not be qualified as a measurable target lesion. (Section 4.2)
- Addition to inclusion criterion 12 of further examples for highly effective hormonal contraceptives. (Section 4.2)
- Revision of the exclusion criterion 10 to exclude the subjects who have received radioimmunotherapy within 3 months prior to the first dose of the investigational product (IP) to allow recovery from possible therapy-associated bone marrow suppression secondary to this treatment. (Section 4.3)
- Clarification that prior exposure to bendamustine is not exclusionary for Arm C dose level 1 (exclusion criterion 12) as bendamustine will not be a part of the investigational combination treatment (ie, durvalumab and rituximab) in this dose level. (Section 4.3)
- Addition of an exception to exclusion criterion 14 to allow the use of pre-phase treatment with corticosteroids (1 mg/kg/day prednisone or equivalent) for a maximum of 7 days prior to Cycle 1 Day 1 for subjects with bulky disease, systemic symptoms, compressive disease, or rapidly progressing adenopathies. (Sections 4.3 and 8)
- Clarification in exclusion criterion 17 that 'well-controlled type 1 diabetes mellitus and hypothyroidism' will not be exclusionary active autoimmune diseases. (Section 4.3)
- Clarification in exclusion criterion 20 that hepatitis B virus (HBV) deoxyribonucleic acid (DNA) testing will not be necessary in subjects who are seropositive for antibody to the hepatitis B surface antigen (anti-HBs) only due to prior exposure or vaccination for consistency with Section 6.1. (Section 4.3)
- Removal of direct thrombin inhibitors (eg, dabigatran) from the exclusion criterion 32 listing the anticoagulant agents which should not be used concomitantly with ibrutinib. (Section 4.3)
- Clarification that the exclusion criteria 27 and 28 will apply only to subjects who will receive rituximab as a part of their study treatment and exclusion criteria 33 only to subjects who will receive bendamustine as a part of their study treatment. (Section 4.3)
- Addition of lipase as a laboratory test to monitor for pancreatitis in addition to amylase for consistency with the dose toxicity and management guidelines. Clarification of B symptoms will be collected. Revision of visit window from ± 2 days to ± 3 days. (Sections 6.1, 6.2, 6.2.1, and 6.3.1 and Tables 7, 8, 9, and 10)
- Clarification that direct antiglobulin test for subjects with CLL will be performed at site's local laboratories. (Section 6.1 and Table 9)

- Clarification that total, direct, and indirect bilirubin will be performed during all relevant visits. (Sections 6.1, 6.2, and 6.2.1)
- Update of the allowed window for the vital signs which will be taken at pre-durvalumab administration as "within an hour prior to start of durvalumab infusion." (Sections 6.2 and Tables 7, 8, 9, and 10)
- Clarification that the follow up for subsequent antilymphoma therapy and overall survival following disease progression may be via telephone and not require a site visit. (Section 6.3.2)
- Addition of the word "interim" to refer to the computed tomography (CT) scans at Cycle 4, 7, 10, or Cycle 14 Day 1/end of durvalumab treatment (EOT-D) referred to in Section 6.4.1.1 for the CT scan time points. (Sections 6.4.1.1 and 6.4.1.2)
- Removal of the fluorodeoxyglucose-positron emission tomography (FDG-PET) planned for Cycle 14 Day 1/end of durvalumab treatment (EOT-D). (Section 6.4.1.2 and Tables 7, 8, 9, and 10)
- Clarification of supporting efficacy assessments (ie, B symptoms, hematology and clinical chemistry laboratories) will be performed until documentation of disease progression. (Section 6 and Tables 7, 8, 9, and 10)
- Clarification that the same imaging modality (eg, CT or MRI) and technique (eg, use of contract, slice thickness for scans) should be used throughout the study. (Section 6.4.1.1 and 6.4.2.1.)
- Clarification that bone marrow disease evaluation is performed at site's local laboratory and MRD at designated analytical laboratories. (Section 6.4.2.2.)
- Update of the pharmacokinetic (PK) and immunogenicity sample collection time point windows to allow greater logistical flexibility. Update of Table 12 with 4 additional durvalumab PK blood draws at the corresponding time points with each immunogenicity sample planned. (Sections 6.6 and 6.7, and Tables 7, 8, 9, 10, 12, 13, 14, and 15)
- Reorganization of Section 6.8 Biomarkers, Pharmacodynamics, Pharmacogenomics for a better read. (Section 6.8.1, 6.8.2 and 6.8.3 and Tables 16, 17, and 18)
- Revision of the specifications for required infusion supplies associated with durvalumab administration based on the Durvalumab Investigator's Brochure. (Section 7.1.1)
- Removal of the instructions for ibrutinib dosing in proximity to food intake based on the approved ibrutinib label. (Section 7.2.1.2.2)
- Dose banding and body surface area capping at 2.0 mg/m^2 are allowed as per local practice. (Section 7.1.3)
- Update to the Dose Treatment Modification and Toxicity Management Guidelines. (Tables 30, 31, 32 and 33)

- Removal of direct thrombin inhibitors from the prohibited concomitant medication with ibrutinib and added investigators should consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and postsurgery depending upon the type of surgery and the risk of bleeding based on the approved ibrutinib label. Update to the allowed timeframe for live attenuated vaccine post durvalumab or rituximab dose. Addition of risk with intrauterine device. (Section 8.2)
- Added liver disease experts will be consulted and HBV DNA will be repeated in case of any elevation in liver enzymes of subjects who are treated with rituximab, bendamustine or lenalidomide for monitoring and treatment management. (Section 8.3.1)
- Specified whether the reporting for each study population will be done against actual treatment received versus planned treatment. Rephrased the biomarker endpoint for clarity. (Section 9)
- Clarification that any serious adverse event (SAE) made known to the investigator at any time beyond the protocol-defined safety follow up period that are suspected of being related to participation in the study (eg, a study-related procedure) should also be reported to Celgene Drug Safety. Addition based on the request received from German Central Ethics Committee that any SAE beyond the protocol-defined safety follow-up period may be reported to Celgene Drug Safety even if not suspected of being related to IP or participation in the study as required by local regulations. (Section 10.5)
- Correction of the reporting requirement for the expedited reporting of adverse events in Japan from biannual to annual. (Section 10.6)
- Update of adverse event of special interest (AESI) section. (Section 10.7)
- Specification of "pregnancy" as a reason for treatment discontinuation. (Section 11)
- Update of the reference list with Bendeka®; Cheson, 2016; Higgs, 2016; and Rizvi, 2015. (Section 17)
- Correction of typographical errors and updated tables and table footnotes to be consistent with the revised text throughout the document.