Official Title of Study:

A Phase 2, Open-label, Multicenter Study to Evaluate the Safety and Clinical Activity of Durvalumab in Combination with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (R-CHOP) or with Lenalidomide plus R-CHOP (R2-CHOP) in Subjects With Previously Untreated, High-Risk Diffuse Large B-Cell Lymphoma

PROTOCOL(S) MEDI4736-DLBCL-001

NCT Number: NCT03003520

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A PHASE 2, OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE SAFETY AND CLINICAL ACTIVITY OF DURVALUMAB IN COMBINATION WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, PREDNISONE (R-CHOP) OR WITH LENALIDOMIDE PLUS R-CHOP (R2-CHOP) IN SUBJECTS WITH PREVIOUSLY-UNTREATED, HIGH-RISK DIFFUSE LARGE B-CELL LYMPHOMA

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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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

Introduction

On 05 Sep 2017, a Partial Clinical Hold was placed to 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 pembrolizumab, an anti-programmed cell death-1 (PD-1) antibody, in patients with multiple myeloma in combination with immunomodulatory agents. As a result, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R-CHOP) after Cycle 1 regardless of diffuse large B-cell lymphoma (DLBCL) cell of origin (COO) subtype. Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, could continue study treatment after being reconsented.

Study enrollment was completed in March 2018.

The protocol-defined primary analysis was completed with a data cutoff date of 02 Aug 2018, and the last subject's last durvalumab dose occurred on 04 Mar 2019. Subsequently, the last durvalumab subject's 90-day Safety Follow-up Visit was completed. At the time of the data cutoff date of the last 90-day Safety Follow-up Visit (06 Jun 2019), 30 subjects were in follow-up. No subjects were on treatment with durvalumab or any other study treatments.

There are no further plans to evaluate long-term efficacy, including overall survival (OS), for the remaining subjects on study, and no additional statistical analysis on safety and efficacy will be performed.

Therefore, the Follow-up Period will be discontinued, and data collection in the clinical database will stop under this amendment. Subjects who received lenalidomide will continue to be followed for second primary malignancies (SPMs) as required by this study protocol (Section 3.1.3.1) [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 2, Open-label, Multicenter Study to Evaluate the Safety and Clinical Activity of Durvalumab in Combination with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (R-CHOP) or with Lenalidomide plus R-CHOP (R2-CHOP) in Subjects With Previously Untreated, High-Risk Diffuse Large B-Cell Lymphoma

Indication

Previously untreated, high-risk DLBCL.

Objectives

- Primary Objective
  - To explore the clinical activity of durvalumab (MEDI4736) in combination with R-CHOP or R2-CHOP followed by durvalumab consolidation therapy in previously untreated subjects diagnosed with high-risk DLBCL

- Secondary Objectives
  - To evaluate the safety and tolerability of durvalumab when given in combination with R-CHOP or R2-CHOP followed by durvalumab consolidation therapy
  - To identify and develop biomarkers of the tumor microenvironment and of the host immune system which are predictive of clinical response to durvalumab, when administered in combination with R-CHOP or R2-CHOP, followed by durvalumab consolidation therapy that will be tested in further randomized clinical trials. Examples of defined analytical methods that may be investigated include, but are not limited to:
    - PD-L1 immunohistochemistry (IHC)
    - Gene Expression Signatures
- Exploratory Objective(s)
  - To examine the pharmacokinetic/pharmacodynamic (PK/Pd) relationship, and the mechanistic biomarkers for durvalumab when given in combination with R-CHOP or with R2-CHOP followed by durvalumab consolidation therapy.
  - To evaluate impact on endpoints related to clinical activity of durvalumab when given in combination with R-CHOP followed by durvalumab consolidation therapy.

Study Design

This Phase 2, two-arm, open-label study is designed to evaluate durvalumab in combination with R-CHOP (Arm A) or in combination with R2-CHOP (Arm B), followed by durvalumab consolidation therapy in previously untreated subjects with high-risk DLBCL (Figure 1).[1] Induction treatment with R-CHOP will last for a total of up to 6 to 8 treatment cycles, and the total time on study treatment, including durvalumab consolidation, will last up to 12 months.

All subjects will be treated with durvalumab combined with R-CHOP during Cycle 1 of induction therapy. Based on their DLBCL COO subtype (ABC versus non-ABC) as determined by the NanoString Lymphoma subtyping test (LST) before start of Cycle 2, subjects will be allocated to one of two treatment arms[1] from Cycle 2 onwards:

Induction Therapy (21-day cycles)

Arm A: Durvalumab in combination with R-CHOP

Durvalumab 1125 mg intravenously (IV) on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R-CHOP (IV rituximab, doxorubicin, vincristine, and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5).

[1] As a result of the US FDA Partial Clinical Hold, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R CHOP) after Cycle 1 regardless of DLBCL COO subtype. Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, could continue study treatment after being reconsented.

Arm B: Durvalumab in combination with R2-CHOP[1]

Durvalumab 1125 mg IV on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R2-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5; daily oral lenalidomide 15 mg from Day 1 to 14) from the cycle following COO determination until end of induction therapy (Cycle 6 or Cycle 8), or starting Cycle 1 if ABC subtype is identified prior to Cycle 1 Day 1 (C1D1).

Consolidation Therapy (28-day cycles) for subjects achieving a sufficient therapeutic response at end of the induction therapy. *Note: In this study, a CR at the end of induction therapy is considered a sufficient therapeutic response. In addition, subjects achieving a PR at the end of induction therapy may continue on consolidation therapy based on the decision of the Investigator.*

Arm A and Arm B:

Durvalumab 1500 mg IV on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1.

All treatments will be administered until disease progression, unacceptable toxicity, or the completion of the treatment regimen. Eligible subjects for whom the COO has already been identified as ABC subtype by the NanoString LST before starting study treatment, may have lenalidomide added starting at C1D1 onwards (Arm B). Subjects for whom the COO is determined as ABC only after Cycle 1 will be allocated to Arm B whenever the results become available, however, missed cycles of lenalidomide will not be made up. [1] Subjects for whom COO determination is inconclusive will continue treatment in study Treatment Arm A. Any newly enrolled subject with DLBCL of ABC COO subtype will continue induction therapy on Arm A (durvalumab + R-CHOP) after Cycle 1.

The study is divided into two stages:

- A *Safety Run-in Stage* to evaluate the safety of the treatment combinations until at least 10 subjects are included. Following Partial Clinical Hold instituted by the US FDA which affects Arm B, the Safety Run-in Stage will evaluate safety of the treatment Arm A combinations when at least 10 subjects have been included into Arm A and have been treated for at least one cycle of study treatment or discontinued prematurely.
- An *Expansion Stage* to analyze the clinical activity of the treatment combinations in up to a total of approximately 40 subjects in the efficacy evaluable population.

A Safety Review Committee (SRC), composed of the Celgene Medical Monitor, the Celgene Drug Safety Physician, as well as selected participating Principal Investigators, will evaluate the safety profile of treatment Arm A combination during the *Safety Run-in Stage*. The decision to initiate enrollment into the *Expansion Stage* will occur at the discretion of the Sponsor following the evaluation of the *Safety Run-in Stage* by the SRC. This review will take place after at least 10 subjects have been enrolled into Arm A and have completed at least one cycle of study treatment or discontinued prematurely.

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

Study Population

The study population will consist of previously untreated subjects with high-risk DLBCL. In this study, high-risk DLBCL is defined as meeting both of the following two criteria:

- Ann Arbor Stage 3-4 or Ann Arbor Stage 2 with bulky disease ≥ 7.0 cm
- Intermediate-high or high International Prognostic Index (IPI) risk:
  IPI ≥ 3 or National Comprehensive Cancer Network-IPI (NCCN-IPI) ≥ 4

This study is expected to be conducted in the US and Europe. Additional study sites located in other regions may be considered for participation as necessary.

Sample Size

Approximately 45 subjects are planned to be enrolled into this study (with approximately 40 subjects in the efficacy evaluable population).

Study Duration for Subjects

The study consists of a Screening Period (up to 28 days before first dose of study treatment), a Treatment Period (up to a total of 12 months) and a Follow-up Period (up to 5 years after the last subject is enrolled).

Follow-up for safety and efficacy begins after study treatments have completed or discontinued. For safety follow-up, subjects are followed for AEs, SPMs, and concomitant medications/ procedures for 90 days after the last durvalumab dose or 28 days after the last dose of other IPs, whichever is the later date. For efficacy follow-up, subjects are followed for disease progression, or until death, lost to follow-up, or consent withdrawal, for up to 5 years after the last subject is enrolled, whichever occurs first.

Following completion of the last durvalumab subject's 90-day safety follow-up (data cutoff date 06 Jun 2019) and discontinuation of the Follow-up Period, subjects are no longer required to be followed for disease progression, safety, and can stop study participation under this amendment. Subjects who received lenalidomide will continue to be followed for up to 5 years from the date of enrollment (C1D1) of the last subject and evaluated for the occurrence of SPMs.

Overview of Key Efficacy Assessments

The response to treatment will be assessed according to the 2014 International Working Group (IWG) Response Criteria for Non-Hodgkin's Lymphoma (NHL) (Cheson, 2014).

Efficacy assessments will include:

- Computed tomography (CT) scans
- Fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans
- Clinical findings (eg physical examination, constitutional symptoms)

Overview of Key Safety Assessments

Safety assessments will include:

- Monitoring for adverse events (AE) including SPM
- Physical examination
- Vital signs
- Body weight
- Eastern Cooperative Oncology Group (ECOG) performance status
- Hepatitis B virus (HBV) serology
- Hematology laboratory parameters (complete blood count [CBC] with differential)
- Serum chemistry laboratory parameters
- Serum immunoglobulins
- Cardiac function/left-ventricular ejection fraction (LVEF)
- Electrocardiogram
- Concomitant medications, therapies, and procedures
- Pregnancy testing (for female subjects of childbearing potential [FCBP] only)

Statistical Methods

The *Safety Run-in Stage* will be used to determine the tolerability of the addition of durvalumab to the induction treatment with R-CHOP until at least 10 subjects have completed at least one cycle of study treatment or discontinued prematurely. Following Partial Clinical Hold instituted by the US FDA which affects Arm B, the Safety Run-in Stage will evaluate safety of the treatment Arm A combinations when at least 10 subjects have been included into Arm A and have been treated for at least one cycle of study treatment or discontinued prematurely. Once treatment is confirmed to be tolerable, additional subjects will be enrolled for the *Expansion Stage* up to a total of approximately 40 subjects in the efficacy evaluable population.

The efficacy evaluable population is defined by all subjects who complete at least one cycle of their assigned treatment, have a baseline assessment by CT scan and have at least one post baseline tumor response assessment.

The primary efficacy analysis will evaluate the complete response rate (CRR) at the end of the induction therapy in the efficacy evaluable population in a comparative manner against historical control. The key secondary efficacy analysis will evaluate the rate of subjects who continue consolidation therapy out of all subjects in the efficacy evaluable population in a comparative manner against historical control.

If null hypothesis on primary endpoint is rejected, hypothesis testing on the key secondary endpoint will be performed hierarchically without any type I error adjustment.

Analysis of secondary efficacy endpoints will include further analysis of response and progression data, and in particular those data related to biomarkers predictive of response to study treatment.

The statistical analysis of the safety profile of the study treatments will be observational in nature.

There is no interim analysis planned in this study.

The primary analysis for this study was completed (data cutoff date: 02 Aug 2018). No additional efficacy or safety statistical analyses are planned.

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1. INTRODUCTION

Any questions regarding the protocol should be directed to the Celgene Medical Monitor or designee.

Please refer to the Investigator's Brochures (IBs) of lenalidomide and durvalumab for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical trials, and AE profiles of these Investigational Products (IP).

On 05 Sep 2017, a Partial Clinical Hold was placed to 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 pembrolizumab, an anti-programmed cell death-1 (PD-1) antibody, in patients with multiple myeloma in combination with immunomodulatory agents. As a result, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R-CHOP) after Cycle 1 regardless of diffuse large B-cell lymphoma (DLBCL) cell or origin (COO) subtype. Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, may continue study treatment after being reconsented.

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1.1. Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma is a distinct histological type within mature B-cell non-Hodgkin's lymphoma (NHL) that accounts for approximately 31% of all newly diagnosed malignant lymphomas (Armitage, 1998), and is characterized by large tumor cells and aggressive clinical behavior.

In most countries worldwide, the standard of care treatment for newly diagnosed DLBCL consists of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy in combination with the anti-CD20 monoclonal antibody rituximab (R-CHOP; Feugier, 2005; Ketterer, 2013). In a study comparing R-CHOP with CHOP as front-line therapy in elderly subjects with DLBCL, treatment with R-CHOP achieved a 5-year event-free survival (EFS) of

47%, a 5-year progression free survival (PFS) of 54%, and a 5-year overall survival (OS) of 58% (Feugier, 2005).

R-CHOP-21 (R-CHOP given in 21-day cycles) as the current standard of care in this disease setting has not been replaced by other treatment regimens including dose-intensified or dose-dense regimens such as dose-intensive rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone (R-ACVBD), dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab (DA-EPOCH-R), rituximab, cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone (R-CHOEP), dose dense regimens (R-CHOP-14; R-CHOP given in 14-day cycles), and rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate cytarabine (R-HyperCVAD) (Ketterer, 2013; Micallef, 2011; Recher, 2011).

Considering the overall DLBCL population, approximately 50% to 60% of patients achieve a long-lasting complete response (CR) following R-CHOP and can be considered cured (Feugier, 2005; Micallef, 2011). In contrast, those 40% to 50% of DLBCL patients who are refractory or who progress or relapse following R-CHOP, have only limited treatment options and a poor overall clinical outcome, most of them dying within two years. Furthermore, DLBCL patients with an increased disease risk (Section 1.2) have a poorer outcome after R-CHOP therapy than the overall DLBCL patient population.

Therefore, patients who do not achieve a durable CR remain an unmet medical need and the evaluation of new treatment strategies is warranted.

1.2. Clinical and Biological Prognostic Factors

1.2.1. International Prognostic Index (IPI) and National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI)

The IPI score (Appendix F) is an important prognostic tool developed utilizing clinical characteristics from more than 1,000 aggressive lymphoma patients treated with CHOP-like chemotherapy (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993). Although developed in the pre-rituximab era, the IPI is still applicable and utilized today. Five clinical characteristics (age, lactic acid dehydrogenase [LDH], number of extra nodal sites, Ann Arbor stage, and ECOG performance status) are used to stratify patients into the following 4 risk categories:

- Low-risk (0-1)
- Low-intermediate risk (2)
- High-intermediate risk (3)
- High-risk (4-5).

The NCCN-IPI scoring system (Appendix F) is an enhanced IPI score developed from clinical data of 1,650 patients with DLBCL treated during the rituximab era between 2000-2010 (Zhou, 2014). Five predictors (age, LDH, sites of involvement, Ann Arbor stage, and ECOG performance status) were identified and a maximum of 8 points assigned, and patients are stratified into the following 4 risk groups as follows:

- Low-risk (0-1)
- Low-intermediate risk (2-3)
- High-intermediate risk (4-5)
- High-risk (6-8).

For this study, patients with either an IPI > 2 and/or NCCN-IPI > 3 will be considered to have high IPI risk. The PFS in this patient population is significantly lower with a 2-year PFS rate of approximately 60-65% compared with 85-90% in patients with low or low-intermediate IPI risk (Sehn, 2007).

1.2.2. Cell of Origin

Diffuse large B-cell lymphoma is composed primarily of two biologically distinct patho-physiologic entities (Alizadeh, 2000) derived from different cells of origin which can be classified by gene expression profiling (GEP): germinal center B-cell (GCB) type and ABC type. Subsequently, an additional type III was identified by GEP (Rosenwald, 2002), which has since been renamed as unclassifiable type. In contrast, the less precise method of immunohistochemistry (IHC) results in grouping ABC and unclassifiable together as the non-GCB type and thus differentiates between GCB and non-GCB only. The Lymphoma/ Leukemia Molecular Profiling Project reported approximately 60% GCB and 40% non-GCB in 240 newly diagnosed DLBCL subject biopsy samples examined by GEP (Fu, 2008; Lossos, 2004; Rosenwald, 2002).

The different DLBCL types have been reported to have different clinical outcomes with CHOP (Rosenwald, 2002) and R-CHOP (Fu, 2008) therapy. In the first-line setting with CHOP therapy, the 5-year OS rates for the GCB, unclassifiable, and ABC types were 60%, 39%, and 35%, respectively (Rosenwald, 2002). With R-CHOP, the 3-year EFS for GCB and non-GCB subtypes was 67% and 52%, respectively, and the 3-year OS was 85% and 69%, respectively (Fu, 2008). With R-CHOP and predominantly higher risk patients (IPI 0-1 = 21%, IPI 2-3 = 63%, and IPI 4-5 = 15%), the median PFS for the ABC type was 1.5 years (Lenz, 2008).

Gene expression profiling on fresh tissue biopsy samples was considered a gold standard for the characterization of the COO in DLBCL. However, defining the COO via GEP is currently neither part of the routine diagnostic work-up in clinical practice, nor a practical method for subject selection in clinical trials due to the requirement of a fresh biopsy sample and the substantial time and technological expertise required to perform standard GEP and analysis.

In this clinical study, a GEP-based assay will be used to identify the COO. The NanoString Lymphoma subtyping test (LST) assay, which is based on the NanoString 20-gene assay for COO subtyping in DLBCL, will be used. The LST assay profiles formalin-fixed paraffin-embedded (FFPE) tissue using the previously reported 20-gene Lymph2Cx algorithm on the nCounter® Dx analysis platform. Although this assay is technically verified, it has not received marketing approval by a health authority beyond being Conformité Européenne (CE) marked in the European Union (EU).

The NanoString 20-gene assay was verified against the original COO model defined by Lenz (Lenz, 2008) using an independent cohort of 68 FFPE biopsies. In the validation cohort, the assay was found to be accurate with only one case with definitive COO that was incorrectly

assigned by NanoString. The assay was also found to be robust with > 95% concordance of COO assignment between two independent laboratories (Scott, 2014b).

The NanoString LST assay is currently being utilized to identify ABC-type DLBCL for participation in a Celgene-sponsored Phase 3 study comparing the safety and efficacy of lenalidomide in combination with R-CHOP (R2-CHOP) to R-CHOP in patients with previously untreated ABC-DLBCL (NCT02285062).

1.2.3. Immune-checkpoint Inhibition

The intratumoral microenvironment in B-cell lymphoma includes tumor-infiltrating lymphocytes (TILs) which are T-cells that appear to be specific for the malignant B-cell clone and, thus, have the capacity to control the growth of the lymphoma (Dunn, 2004, Gooden, 2011). However, these T-cells have been found to have decreased proliferative capacity and effector function (Gitelson, 2002, Hilchey, 2009), which could explain their inability to attack and eradicate the malignant B cells. Chronic and prolonged activation may cause some T-cells to become "exhausted" and other T-cells to acquire expression of inhibitory receptors (eg programmed cell death-1 [PD-1], programmed cell death ligand-1 [PD-L1]) and become suppressive cells (Zhi-Zhang, 2015), a phenomenon also known as "adaptive immune resistance" (Tumeh, 2014). 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).

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).

1.2.4. PD-L1/PD-1 Pathway in B-cell Malignancies

A large French multicenter clinical trial demonstrated that high plasma levels of soluble PD-L1 are a predictive biomarker associated with a poorer overall survival (OS) in DLBCL patients treated with R-CHOP (Rossille, 2014). These findings were confirmed in two additional databases in Australia and the U.S. and were found to be independent of IPI and other clinical factors (Fest, 2014).

Furthermore, it has been shown that PD-L1 expression on DLBCL cells is an independent (negative) prognostic factor for OS and that the number of PD-1 positive TILs is significantly associated with PD-L1 positivity of lymphoma cells and tumor infiltrating non-malignant stromal cells (Kiyasu, 2015). In addition, PD-1 expression in peripheral blood CD4+ and CD8+ T-cells were found to be markedly different between chronic lymphocytic leukemia (CLL) disease stages when compared with healthy subjects (Novak, 2015).

A preclinical mantle-cell lymphoma (MCL) 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 clinical studies, nivolumab (Lesokhin, 2014) has shown single-agent activity in clinical studies in patients with DLBCL, follicular lymphoma (FL) and T-cell lymphomas.

1.3. Compound Background

1.3.1. Durvalumab (MEDI4736)

Durvalumab (MEDI4736) is a human immunoglobulin (Ig) G1κ monoclonal antibody (mAb) that blocks PD-L1 by inhibiting binding to its receptors, allowing T-cells to recognize and kill tumor cells. Durvalumab selectively binds to human PD-L1 with high affinity blocking its ability to bind to PD-1 and cluster of differentiation (CD) 80. 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 patients 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 IB for further information.

1.3.2. Lenalidomide

Lenalidomide (Revlimid®) is a member of the class of 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:

- Multiple myeloma (MM) in combination with dexamethasone
- Maintenance MM therapy following autologous hematopoietic stem cell transplantation
- Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities
- MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib

In Europe, lenalidomide has been approved for the treatment of patients with:

- As combination therapy in patients with previously untreated MM who are not eligible for transplant
- In combination with dexamethasone for patients with MM who have received at least one prior therapy
- As maintenance monotherapy in the treatment of newly diagnosed patients with MM who have undergone autologous stem cell transplantation

- 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
- Relapsed or refractory MCL

Please refer to the lenalidomide IB for further information.

1.4. Rationale

1.4.1. Rationale for Study Design

Patients with high-risk DLBCL typically have insufficient therapeutic outcomes. Therefore, the addition of novel agents to the currently used induction therapy (R-CHOP backbone) is a rationale approach to improve therapeutic outcomes in this disease setting.

1.4.2. Rationale for Backbone Therapy (R-CHOP, R2-CHOP)

Treatment with R-CHOP is currently the most commonly used induction therapy for patients with previously untreated DLBCL.

Patients with non-GCB-DLBCL have a worse outcome than GCB-like DLBCL when treated with R-CHOP. Importantly, clinically meaningful improvements in CR rate and PFS were seen in two recent Phase 2 trials in patients with non-GCB-DLBCL who were treated with lenalidomide in combination with R-CHOP (R2-CHOP) when compared with historical R-CHOP-21 data (Nowakowski, 2015; Chiapella, 2012).

In the REAL07 Phase 2 study with R2-CHOP conducted by the Italian Lymphoma Study Group FIL (Chiapella, 2012; Vitolo, 2014), Overall Response Rate was 92% and the CR rate was 86%. The 2-year PFS was 81% (95% confidence interval [CI], 51% to 93%) in patients with non-GCB disease and 71% (95% CI, 51% to 93%) in those with GCB disease (HR 0.78, 95% CI, 0·21 to 2·90; p=0.705).

In a Phase 2 study with R2-CHOP conducted by the Mayo Clinic (Nowakowski, 2015), the overall response rate (ORR) was 98% with a CR rate of 80%. Event-free survival and overall survival (OS) rates at 24 months were 59% (95% CI, 48 to 74) and 78% (95% CI, 68 to 90), respectively.

In a historical comparison with patients treated with R-CHOP, the 24-month progression-free survival (PFS) and OS were 28% versus 64% and 46% versus 78% in non-GCB DLBCL versus GCB DLBCL, respectively, underlining the worse outcome of non-GCB-DLBCL patients who are treated with R-CHOP.

In contrast, no significant changes in outcome were noted in GCB-like DLBCL patients receiving R2-CHOP. When compared with patients treated with R-CHOP, there was no difference in 24-month PFS or OS for R2-CHOP patients on the basis of non-GCB and GCB subtype (60% versus 59% and 83% versus 75%, respectively).

Based on these promising Phase 2 results, in this study R-CHOP will be used as backbone therapy for patients with the non-ABC subtype whereas R2-CHOP will be used for patients with the ABC subtype. Following Partial Clinical Hold instituted by the US FDA rationale for backbone therapy has been changed. Any newly enrolled subject with ABC subtype will be

treated with R-CHOP. Activated B-cell (ABC) subtype subjects already treated with R2-CHOP may continue study treatment if receiving clinical benefit, based on the discretion of the Investigator and after being reconsented.

1.4.3. Rationale for Investigational Product

Based on the described pre-clinical and clinical observations related to the PD-1/PD-L1 pathway, it is hypothesized that durvalumab will have activity in DLBCL. In particular, the addition of durvalumab may significantly augment the anti-tumor activity of R-CHOP against high-risk DLBCL subtypes.

The safety of durvalumab has already been explored and assessed in other hematology and oncology patient populations, and no dose limiting toxicity (DLT) has been defined to date. However, as there is limited clinical experience with durvalumab as monotherapy in DLBCL and none with durvalumab in combination with R-CHOP or R2-CHOP as first-line therapy of DLBCL, the design of this Phase 2 study includes a *Safety Run-in Stage*.

1.4.4. Rationale for Dose, Schedule, and Regimen

The dosing schedule of 20 mg/kg once every 4 weeks (Q4W) for durvalumab was selected based on the safety analysis of doses (0.1, 0.3, 1, 3, and 10 mg/kg once every 2 weeks [Q2W]) administered in Study CD ON-MEDI4736-1108 and pharmacokinetics (PK) profile simulations for durvalumab administered using 10 mg/kg Q2W and 20 mg/kg Q4W schedules.

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 (5^{th} median, and 95^{th} 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). Simulation results of 1,000 patients using body weights ranging from 40 to 120 kg demonstrated 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.

As it is therefore considered feasible to use a fixed-dosing regimen, and as a fixed-dosing approach is generally preferred by the prescribing community due to ease of use and reduced dosing errors, the current study will use a fixed dose of 1125 mg durvalumab Q3W (21-day cycles during induction therapy) and 1500 mg durvalumab Q4W (28-day cycles during consolidation therapy), both being equivalent to 20 mg/kg Q4W.

1.4.5. Rationale for Biomarkers

The key specific translational question in this study is whether the COO status or other biomarkers in DLBCL are associated with response to durvalumab in combination with either R-CHOP or R2-CHOP.

1.4.5.1. Rationale for 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. In addition, 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 interferon [IFN]γ gene expression in pretreatment tumor biopsies may predict the best response to durvalumab monotherapy (Higgs, 2015, Higgs 2016).

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.

The predictive biomarker data analysis will proceed in three stages. In the first stage, publically available data, literature, and proprietary data assets of relevance will be analyzed to generate and refine predictive biomarker hypotheses. During the second stage, biomarker data will be analyzed as it is generated for this study and pre-specified hypotheses-related predictive biomarkers and immune mechanism of action will be tested. Lastly, after the biomarker, clinical and outcome data from the study is completed, final conclusions will be made on the pre-specified hypotheses and hypotheses for testing in future studies will be defined.

1.4.5.2. Rationale for Pharmacodynamic Biomarker Assays

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 non-small cell lung cancer (NSCLC) patients demonstrated a statistically significant increase in CD8+ infiltrating lymphocytes from on-treatment tumor samples compared with pre-treatment biopsies (Rizvi, 2015). Furthermore, durvalumab treatment induced IFNγ and effector T cell and Th-1 gene expression within NSCLC biopsies within 8 weeks of treatment (Higgs, 2016), indicating a higher level of tumor microenvironment.

This data is consistent with the Pd effects observed in tumor biopsies from patients treated with atezolizumab (a PD-L1 inhibitor) and pembrolizumab (a 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 pharmacodynamic 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 may also allow new biomarker development to drive clinical decisions early in patients' treatment and could reveal new targets/additional immune system pathways that may be targeted to improve therapeutic outcomes.

2. STUDY OBJECTIVES AND ENDPOINTS

Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, could continue study treatment after being reconsented. Any subject enrolled after the US FDA Partial Clinical Hold received induction therapy on Arm A (durvalumab + R-CHOP) after Cycle 1 regardless of DLBCL COO subtype.

After the last durvalumab subject's 90-day safety follow-up (data cutoff date 06 Jun 2019), the Follow-up Period will be discontinued. Subjects who received lenalidomide will continue to be followed for SPMs as required by this study protocol (Section 3.1.3.1) [redacted].

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to explore the clinical activity of durvalumab (MEDI4736) in combination with R-CHOP or R2-CHOP followed by durvalumab consolidation therapy in previously untreated subjects diagnosed with high-risk DLBCL.
Secondary Objectives
The secondary objectives of the study are: • To evaluate the safety and tolerability of durvalumab when given in combination with R-CHOP or R2-CHOP followed by durvalumab consolidation therapy. • To identify and develop biomarkers of the tumor microenvironment and of the host immune system which are predictive of clinical response to durvalumab, when administered in combination with R-CHOP or R2-CHOP, followed by durvalumab consolidation therapy that will be tested in further randomized clinical studies. Examples of defined analytical methods that will be investigated may include, but are not limited to: – PD-L1 IHC – Gene Expression Signatures
Exploratory Objective
The exploratory objectives of the study are: • To examine the pharmacokinetic/pharmacodynamic (PK/Pd) relationship, and the mechanistic biomarkers for durvalumab when given in combination with R-CHOP or with R2-CHOP followed by durvalumab consolidation therapy. • To evaluate impact on endpoints related to clinical activity of durvalumab when given in combination with R-CHOP followed by durvalumab consolidation therapy.

ABC = activated B-cell; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; DLBCL = diffuse large B-cell lymphoma; IHC = immunohistochemistry; PD-L1 = programmed cell death-ligand 1; PK/Pd = pharmacokinetic/pharmacodynamic; R-CHOP = Rituximab plus CHOP; R2-CHOP = Rituximab and lenalidomide plus CHOP.

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary Endpoint			
Efficacy	Complete response rate (CRR) at end of induction therapy.	Subjects being in CR at the end of induction therapy	6 to 8 cycles (4 to 6 months) after the first dose of any IP
Key Secondary Endpoints			
Efficacy	Rate of subjects who continue consolidation therapy	Subjects being in CR/PR at the end of induction therapy and who continue into consolidation therapy	6 to 8 cycles of induction therapy and at least 1 cycle of consolidation therapy (4 to 6 months) after the first dose of any IP.
Secondary Endpoints			
Biomarker	Clinical response to study treatment in biomarker-defined subpopulations	Identification and development of biomarkers predictive of clinical response to study treatment Defined analytical methods will be used in order to refine those biomarkers to be tested in further randomized clinical studies	Tumor samples at baseline and during study treatment. Peripheral blood samples collected at Screening and during study treatment.
Safety	TEAEs	Incidence of TEAE based on total events, percentage of subjects experiencing any specific TEAE and severity of the TEAE using the NCI-CTCAE criteria V4.03, and V3.0 for Tumor Flare Reaction.	From the first dose of any IP until 90 days after the last dose of durvalumab or 28 days after the last dose of any other IP, whichever is later
Exploratory Endpoints			
Efficacy	PFS at 12 months	Subjects who have not experienced disease progression or death within 12 months after start of study treatment	12 months after the first dose of any IP
Efficacy	PFS at 24 months	Subjects who have not experienced disease progression or death within 24 months after start of study treatment	24 months after the first dose of any IP
Efficacy	CRR at 12 months	Subjects being in complete response (CR) at 12 months after start of study treatment	12 months after the first dose of any IP

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Pharmacodynamic and mechanistic biomarkers of durvalumab	Pd	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.	Before and during study treatment
Pharmacokinetics/ Pharmacodynamics	PK/Pd	Exploration of the PK/Pd relationship of durvalumab when given in combination with R-CHOP and R2-CHOP as induction therapy as well as when administered as consolidation therapy	During study treatment

CR = Complete Response; CRR = Complete Response Rate; IP = Investigational Product; NCI-CTCAE; National Cancer Institute Common Terminology Criteria for Adverse Events; Pd = Pharmacodynamics; PFS = Progression-free Survival; PK =Pharmacokinetics; R-CHOP = Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; R2-CHOP = Lenalidomide plus R-CHOP; sPD-L1 = soluble Programmed Cell Death-Ligand 1; TEAE = Treatment-emergent Adverse Events.

3. OVERALL STUDY DESIGN

The 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

This Phase 2, two-arm, open-label study is designed to evaluate durvalumab in combination with R-CHOP (Arm A) or in combination with R2-CHOP (Arm B), followed by durvalumab consolidation therapy in previously untreated subjects with high-risk DLBCL (Figure 1).[2] Induction treatment with R-CHOP will last for a total of up to 6 to 8 treatment cycles, and the total time on study treatment, including durvalumab consolidation, will last up to 12 months.

The study is divided into two stages:

- A *Safety Run-in Stage* to evaluate the safety of the treatment combinations (by a Safety Review Committee [SRC], see Section 6.5.2) until at least 10 subjects are included in the *Safety Run-in* (see Section 6.5.1). Following Partial Clinical Hold instituted by the US FDA which affects Arm B, the Safety Run-in Stage will evaluate safety of the treatment Arm A combinations when at least 10 subjects have been included into Arm A and have been treated for at least one cycle of study treatment or discontinued prematurely.
- An *Expansion Stage* to analyze the clinical activity of the treatment combinations in up to approximately 40 total subjects in the efficacy evaluable population.

Approximately 45 subjects are planned to be enrolled into this study (with approximately 40 subjects in the efficacy evaluable population). Subjects will be assigned into the appropriate treatment arms dependent upon their COO status as determined by GEP.[2]

3.1.1. Screening Period

The Screening Period begins once the subject signs the written informed consent form (ICF). During this period, the subjects will undergo assessments, according to Table 3 and Section 6.1 to determine whether the subject meets the eligibility criteria described in Section 4.2.

All Screening assessments must be completed within 28 days prior to the first dose of IP administered on C1D1. Subjects must undergo incisional or excisional biopsies of their lymphoma in order to evaluate their tumor microenvironments as well as other biomarkers. A core needle biopsy with multiple passes is acceptable but not preferred, due to the amount of tissue required needed to perform the necessary analyses. For subjects unable to provide fresh tissue samples, an archival diagnostic lymph node/tumor formalin fixed paraffin embedded

[2] As a result of the US FDA Partial Clinical Hold, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R CHOP) after Cycle 1 regardless of DLBCL COO subtype. Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, could continue study treatment after being reconsented.

(FFPE) biopsy obtained prior to signing informed consent may be acceptable for enrollment of a subject with poorly accessible tumor.

3.1.2. Treatment Period

Eligible subjects with previously untreated, high-risk DLBCL will receive one cycle of induction therapy of durvalumab in combination with R-CHOP. Based on their DLBCL COO subtype (ABC versus non-ABC) as determined by the NanoString LST assay before start of Cycle 2, subjects will then be allocated to one of two treatment arms from Cycle 2 onwards (or the cycle following COO determination). Eligible subjects for whom the COO has already been identified as ABC subtype by NanoString LST assay before starting study treatment, may have lenalidomide added starting with C1D1 onwards. Subjects for whom COO determination is inconclusive will continue treatment in study Treatment Arm A. Subjects for whom the COO is determined as ABC only after Cycle 2 will be allocated to Arm B whenever the results become available, however, missed cycles of lenalidomide will not be made up. After the US FDA Partial Clinical Hold, enrollment of new subjects into Arm B was discontinued. If receiving clinical benefit at the discretion of the Investigator, subjects could continue treatment in Arm B after being reconsented. Any newly enrolled subject with DLBCL of ABC COO subtype after the US FDA Partial Clinical Hold could continue induction therapy on Arm A after Cycle 1.

Induction treatment will be administered until disease progression, unacceptable toxicity or the completion of induction treatment (6 to 8 cycles). Subjects completing the R-CHOP-based induction chemotherapy and achieving a CR (or a PR if the Investigator considers this to be a sufficient therapeutic response) will then receive consolidation therapy comprised of durvalumab monotherapy for up to a total of 12 months from the date of C1D1, ie, from the start of the induction treatment period (Figure 1). Subjects receiving lenalidomide will be followed for SPM for 5 years following enrollment (C1D1) of the last subject enrolled into Arm B (Figure 1).

3.1.2.1. Treatment Arms

Study treatment in both arms will be administered in 21-day cycles during the induction treatment and 28-day cycles during the consolidation treatment as follows:

Induction Therapy (21-day cycles)[3]

Arm A: Durvalumab in combination with R-CHOP

Durvalumab 1125 mg intravenously (IV) on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5).

Arm B: Durvalumab in combination with R2-CHOP[3]

Durvalumab 1125 mg IV on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R2-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily

[3] As a result of the US FDA Partial Clinical Hold, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R CHOP) after Cycle 1 regardless of DLBCL COO subtype. Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, could continue study treatment after being reconsented.

oral/IV prednisone/prednisolone from Day 1 to 5; daily oral lenalidomide 15 mg from Day 1 to 14) from the cycle following COO determination until end of induction therapy (Cycle 6 or Cycle 8), or starting Cycle 1 if ABC subtype is identified prior to C1D1.

Consolidation Therapy (28-day cycles)

Arm A and Arm B: (Initiated following induction therapy and CR/PR)

Durvalumab 1500 mg IV on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1 of induction therapy.

3.1.3. Follow-up Period

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

Once all study treatments have been discontinued, subjects will be followed for disease progression or until death, lost to follow-up, or consent withdrawal, for up to 5 years after the last subject is enrolled (C1D1), whichever occurs first.

Subjects receiving lenalidomide will be followed for up to 5 years from the date of enrollment (C1D1) of the last subject and evaluated for the occurrence of SPM.

3.1.3.1. Safety Follow-up

All subjects will be followed for AEs and concomitant medications/procedures until 90 days after the last dose of durvalumab or 28 days after the last dose of any other IP, whichever is later.

Subjects who receive lenalidomide will, in addition to the above, be followed for SPM for up to 5 years from the date of enrollment (C1D1) of the last subject to be treated with lenalidomide.

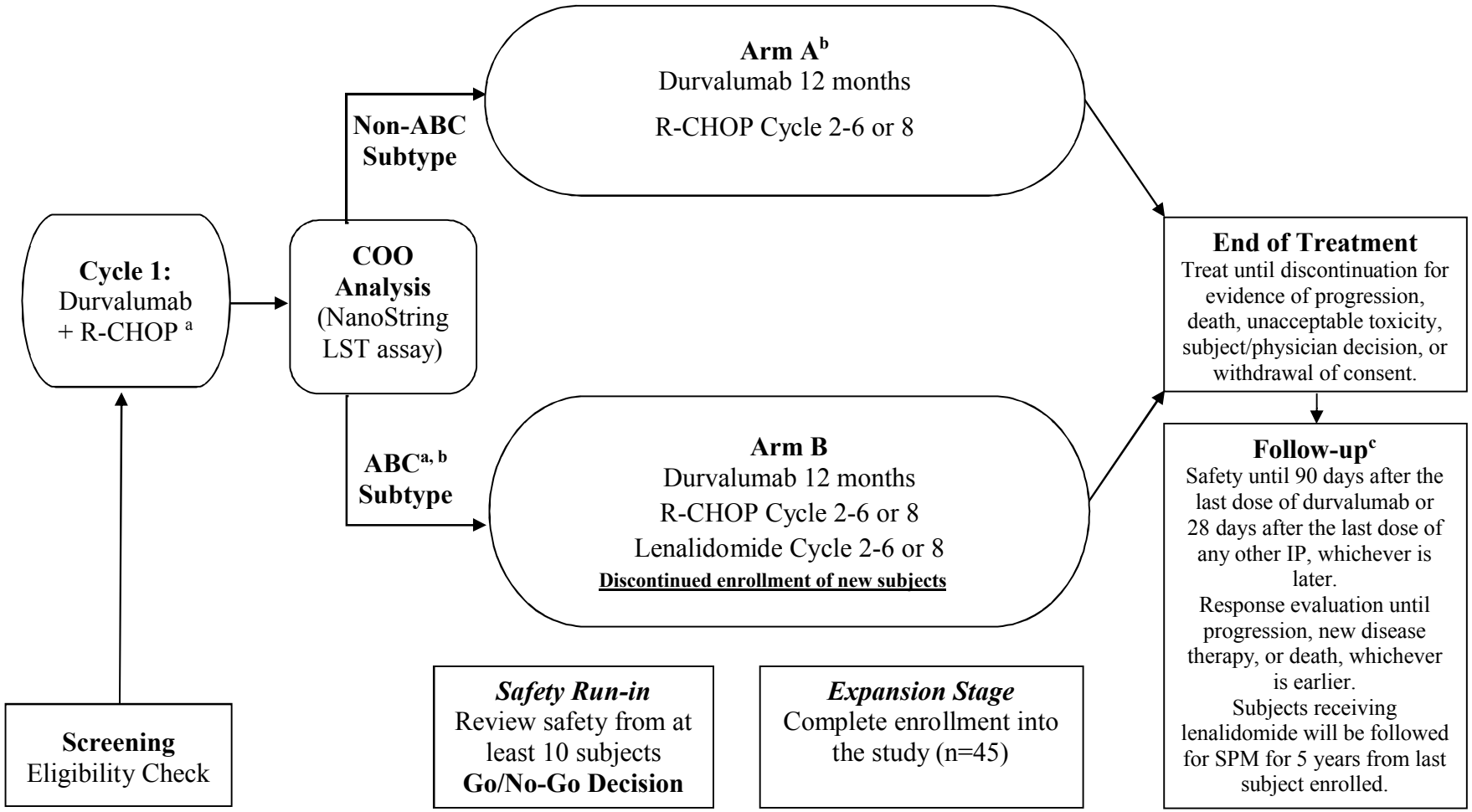
3.1.3.2. Efficacy (Long-term) Follow-up

Subjects will continue to be followed for efficacy following study treatment completion or discontinuation for 5 years after the last subject is enrolled. This includes subjects who complete the full course of treatment, discontinue treatment due to progression or toxicity, as well as those who discontinue before progression to pursue a new anti-lymphoma therapy.

Subjects will be followed for progression, and subsequent anti-lymphoma therapy according to the schedule described in Section 6.3.2. Therefore, efficacy assessments will continue at the protocol-specified time points until first progression or the start of a new anti-lymphoma therapy.

Following completion or discontinuation of durvalumab therapy per protocol for all subjects and completion of the last durvalumab subject's 90-day Safety Follow-up Visit (data cutoff date 06 Jun 2019), subjects are no longer required to be followed for disease progression, subsequent anti-lymphoma therapy, and overall survival. Follow-up procedures, efficacy assessments, central labs, imaging, AEs/SAEs and survival data will no longer be collected in the CRFs.

Figure 1: Study Design



ABC = activated B-cell; COO = cell of origin; DLBCL = diffuse large B-cell lymphoma; IP = investigational product; LST = lymphoma subtyping test; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SPM = second primary malignancy.

[a] Eligible subjects for whom the COO has already been identified as ABC subtype by gene expression profile before starting study treatment, may have lenalidomide added starting with Cycle 1 Day 1 onwards (Arm B).

[b] After the US FDA Partial Clinical Hold enrollment of new subjects into Arm B has been discontinued. If receiving clinical benefit at the discretion of the Investigator, subjects may continue treatment in Arm B after being reconsented. Any newly enrolled subject with DLBCL of ABC COO subtype after US FDA Partial Clinical Hold will continue induction therapy on Arm A after Cycle 1.

[c] Following completion or discontinuation of durvalumab therapy per protocol for all subjects and completion of the last durvalumab subject's 90-day Safety Follow-up Visit (data cutoff date 06 Jun 2019), subjects are no longer required to be followed for disease progression, subsequent anti-lymphoma therapy, and overall survival.

3.2. Study Duration for Subjects

The study consists of a Screening Period (up to 28 days before first dose of study treatment), a Treatment Period (up to a total of 12 months from first dose) and a Follow-up Period (up to 5 years after the last subject is enrolled).

3.3. End of Study

The End of Study 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 pre-specified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 45 subjects with previously untreated, high-risk DLBCL will be enrolled into this study (with approximately 40 subjects in the efficacy evaluable population). This study is expected to be conducted in the US and Europe. Additional study sites located in other regions may be considered for participation as necessary.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is at least 18 years of age at the time of signing the informed consent form (ICF).
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 documented histologically confirmed CD20+ DLBCL of the below World Health Organization (WHO) sub-classifications:
   a. Not otherwise specified (NOS)
   b. Associated with chronic inflammation
   c. Epstein-Barr virus positive (EBV+) of the elderly
   d. T-cell/histiocyte-rich
5. Subject has high-risk disease defined as:
   a. Ann Arbor stage 3-4 or Ann Arbor stage 2 with bulky disease (tumor diameter ≥ 7.0 cm)
   and
   b. Intermediate-high or high disease risk (IPI ≥ 3 or NCCN-IPI ≥ 4; see Appendix F).
6. Subject has bi-dimensionally measurable disease on cross-sectional imaging by CT with at least one (post-biopsy) nodal or extranodal lesion ≥ 2.0 cm in its longest dimension.
7. Subject has not received prior anti-lymphoma treatment. However, for subjects with bulky disease, systemic symptoms, compressive disease, or rapidly progressing adenopathies, pre-phase treatment with up to 100 mg/day prednisone, or equivalent, for a maximum of 7 days is permitted prior to beginning the Treatment Period, at the discretion of the Investigator. A washout period does not apply.
8. Subject is willing and able to undergo tumor/lymph node biopsy during the Screening Period, during treatment when clinically feasible, and at the time of disease progression from subjects who have achieved objective response (CR or partial response [PR]) to study treatment.

   Note: An archival diagnostic lymph node/tumor formalin fixed paraffin embedded (FFPE) biopsy acquired by a surgical or core needle biopsy prior to signing informed consent may be acceptable for enrollment of a subject with poorly accessible tumor.

9. Subject is considered an appropriate candidate for induction therapy with 6 to 8 cycles of R-CHOP immuno-chemotherapy.
10. Subject has a performance status of 0-2 according to the Eastern Cooperative Oncology Group (ECOG) scale.
11. Subject must fulfill the following laboratory requirements:
    a. Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3 (1.5 x 10^9/L) unless secondary to bone marrow involvement by lymphoma (> 50%) as demonstrated by recent bone marrow aspiration and bone marrow biopsy. In the case of documented bone marrow involvement an ANC ≥ 1,000 cells/mm^3 (1.0 x 10^9/L) is required.
    b. Platelet count ≥ 75,000/mm^3 (75 x 10^9/L) unless secondary to bone marrow involvement by lymphoma (> 50%) as demonstrated by recent bone marrow aspiration and bone marrow biopsy. In the case of documented bone marrow involvement a platelet count of ≥ 50,000/ mm^3 (50 x 10^9/L) is required.
    c. Hemoglobin ≥ 10.0 g/dL (6.2 mmol/L) unless secondary to bone marrow involvement by lymphoma (> 50%) as demonstrated by recent bone marrow aspiration and bone marrow biopsy. In the case of documented bone marrow involvement a hemoglobin value of ≥ 9 g/dL is required.
    d. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≤ 2.5 x upper limit of normal (ULN). In the case of documented liver involvement by lymphoma, ALT/SGPT and AST/SGOT must be≤ 5.0 x ULN.
    e. Serum total bilirubin ≤ 2.0 mg/dL (34 µmol/L). In the case of Gilbert's Syndrome, or documented liver or pancreatic involvement by lymphoma, serum total bilirubin must be ≤ 5.0 mg/dL (86 µmol/L).
    f. Calculated creatinine clearance of ≥ 40 mL/min by the Cockcroft-Gault formula. A 24-hour urine collection may also be used for calculating the creatinine clearance value.
12. Females of childbearing potential (FCBP[4]) must:
    a. Have two negative pregnancy tests as verified by the Investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence[5] from heterosexual contact.
    b. Either commit to true abstinence[5] from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, 2 effective measures of contraception without interruption. Contraception methods must include 1 highly effective and 1 additional effective (barrier) method of contraception from at least 28 days prior to starting investigational product, during the study therapy including dose interruptions, and for 1 year following the last dose

[4] A female 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).

[5] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. In contrast, periodic abstinence (eg calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

of rituximab (according to the Rituxan Prescribing Information), 28 days following the last dose of lenalidomide, or 90 days after the last dose of durvalumab, whichever is latest. Cessation of contraception after this point should be discussed with a responsible physician.

Note: Highly effective methods (defined as one that results in a low failure rate [ie, less than 1% per year] when used consistently and correctly). The following are examples of highly effective and additional effective methods of contraception:

Highly effective methods:

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

iii. *Tubal ligation*

iv. *Partner's vasectomy*

Additional effective methods:

v. *Male condom*

vi. *Diaphragm*

vii. *Cervical cap*

c. Agree to abstain from breastfeeding during study participation and for at least 28 days after the last dose of lenalidomide or 90 days after the last dose of durvalumab or 12 months after the last dose of rituximab, whichever is longer.
d. Refrain from egg cell donation while taking durvalumab and for at least 28 days after the last dose of lenalidomide or 90 days after the last dose of durvalumab, whichever is longer.

13. Male subjects must:

a. Practice true abstinence[5] (which must be reviewed on a monthly basis) or agree to use a condom (Appendix E) during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days after the last dose of lenalidomide or 90 days after the last dose of durvalumab, whichever is longer, even if he has undergone a successful vasectomy.
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.

14. 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.

4.3. Exclusion Criteria

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

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Subject 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.
3. Subject has any condition that confounds the ability to interpret data from the study.
4. The following WHO subcategories of DLBCL:
   a. Active central nervous system (CNS) or meningeal lymphoma
   b. Primary cutaneous, leg type
   c. Primary mediastinal (thymic)
   d. Lymphomatoid granulomatosis
   e. Anaplastic lymphoma kinase-positive (ALK)-positive lymphoma
   f. Plasmablastic lymphoma
   g. Large B-cell lymphoma arising in HHV8 associated multicentric Castleman disease
   h. Primary effusion lymphoma
   i. Intravascular large B-cell
   j. B-cell unclassifiable cases with features intermediate between DLBCL and Burkitt's lymphoma
   k. Unclassifiable cases with features intermediate between DLBCL and classical Hodgkin's lymphoma.
5. Subject has evidence of composite DLBCL and Follicular Lymphoma (FL), or of transformed NHL.
6. Subjects with primary CNS lymphoma or secondary CNS involvement by lymphoma. Subjects will be evaluated to assess the status and risk of CNS disease. Risk evaluation of CNS involvement in selected subjects is found in Section 6.1 and the NCCN guidelines, Version 2 (2015), for DLBCL and NHL for risk evaluation of CNS involvement:
   a. Subjects with confirmed CNS involvement of DLBCL will not be eligible
   b. For selected subjects at risk for occult CNS disease, the subject is required to have a negative cerebrospinal fluid (CSF) by cytology examination, routine studies to include cytology, and flow cytometric analysis. A brain/spinal CT or magnetic resonance imaging (MRI) during Screening will be required to rule out CNS disease only in subjects with neurological findings on exam or review of symptoms suspicious for CNS disease
   c. Lumbar puncture is required for selected subjects at risk for occult CNS lymphomatous involvement
   d. All subjects considered to be at high risk for CNS disease MUST be willing to receive CNS prophylaxis according to Section 8.3.2

7. Subject is seropositive for or has active viral infection with hepatitis B virus (HBV):
   a. HBV surface antigen (HBsAg) positive
   b. HBV surface antigen (HBsAg) negative, HBV surface antibody (anti-HBs) positive and/or HBV core antibody (anti-HBc) positive, and detectable viral DNA

   Note: Subjects who are seropositive because of a successfully treated, prior infection are eligible (HBsAg negative, anti-HBs positive, and/or anti-HBc positive, but viral DNA negative). Subjects who are seropositive because of HBV vaccination are eligible (anti-HBs positive, anti-HBc negative, and HBsAg negative).
8. Subject known to be seropositive for hepatitis C virus (HCV) with chronic hepatitis C, or subjects with an active hepatitis C infection requiring anti-viral medication (at time of enrollment).

   Note: HCV positive subjects who do not have active hepatitis C, and who are otherwise acceptable candidates for R-CHOP chemotherapy, as documented by the Investigator, are eligible.
9. Subject known to be seropositive for or active viral infection with human immunodeficiency virus (HIV).
10. Subject has undergone major surgery (excluding lymph node or bone marrow biopsy) within 28 days from signing the informed consent document, unless the subject is recovered.
11. Subject with a life expectancy < 6 months.
12. Subject has a history of other malignancies, unless the subject has been free of the disease for ≥ 5 years. Exceptions to the ≥ 5-year time limit include history of the following:
    a. Localized non-melanoma skin cancer
    b. Carcinoma in situ of the cervix
13. Subject has a contraindication to any drug of the R-CHOP immune-chemotherapy regimen.
14. Left ventricular ejection fraction (LVEF) < 50% as assessed by multi gated acquisition scan (MUGA) or echocardiogram (2-D ECHO), or LVEF < local institutional normal limits for R-CHOP administration as assessed by echocardiography.
15. Subject has peripheral neuropathy ≥ Grade 2.
16. Subject with prior use of lenalidomide.
17. Subject with known allergy to thalidomide.
18. Subject with known sensitivity or allergy to murine products.
19. Subject with use of any investigational agent within 28 days or five half-lives, whichever is longer, prior to first dose of study drug treatment.
20. Subjects with a high risk of developing thromboembolic events, who are unwilling to take venous thromboembolism (VTE) prophylaxis.
21. Females who are pregnant or breastfeeding.

22. Subject having received any prior mAb against CTLA-4, PD-1, or PD-L1.
23. Subject 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 last dose of durvalumab, whichever is longer.
24. Subject with active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis with the exception of a prior episode that has resolved or diverticulosis, celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea; systemic lupus erythematosus; Wegener's syndrome [granulomatosis with polyangiitis]; myasthenia gravis; Graves' disease; rheumatoid arthritis; hypophysitis, uveitis; etc.) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
    a. Subjects with vitiligo or alopecia.
    b. Subjects with hypothyroidism (eg following Hashimoto syndrome) stable on hormone replacement.
    c. Subjects with psoriasis not requiring systemic treatment.
25. Subject with current or prior use of immunosuppressive medication within 28 days prior to the first dose of durvalumab. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical or local steroid injections (eg intra-articular injection);
    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent;
    c. Steroids as premedication for hypersensitivity reactions (eg CT scan premedication).
26. Prior organ transplantation including allogeneic stem cell transplantation.

5. TABLE OF EVENTS

Table 3: Schedule of Assessments

EVENTS	Screening	INDUCTION																	CONSOLIDATION									EOT (PD)	Safety FU		Efficacy FU[j]
Cycle		1			2		3		4		5		6		7		8		EOI 1	2	3	4	5	6	7	8	9				90d up to 2 years from C1D1
Planned Day	-28 to-1	1	8	15	1	15	1	15	1	15	1	15	1	15	1	15	1	15	1	1	1	1	1	1	1	1	1		IP +28d	Dur +90d	
Window (± day)		2	1	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	7	2	2	2	2	2	2	2	2	7	7	14	14
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion / exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Disease and medical history (including HIV /HCV)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior cancer therapies	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Central Nervous System (CNS) Lymphoma evaluation	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hepatitis B Virus (HBV) Local Testing	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Electrocardiogram	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	X	-	-	-
Left-ventricular ejection fraction	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	X	-	-	-
SAFETY ASSESSMENTS																															
Adverse Events	From signing ICF and until 90 days after the last dose of durvalumab or 28 days after the last dose of any other IP																														
Assessment of Second Primary Malignancy (SPM)	From signing ICF for up to 90 days after the last dose of durvalumab and up to 5 years after enrollment (C1D1) of the last subject to receive lenalidomide																														

Table 3: Schedule of Assessments (Continued)

EVENTS	Screening	INDUCTION																	CONSOLIDATION									EOT (PD)	Safety FU		Efficacy FU[j]
Cycle		1			2		3		4		5		6		7		8		EOI 1	2	3	4	5	6	7	8	9				90d up to 2 years from C1D1
Planned Day	-28 to-1	1	8	15	1	15	1	15	1	15	1	15	1	15	1	15	1	15	1	1	1	1	1	1	1	1	1		IP +28d	Dur +90d	
Window (± day)		2	1	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	7	2	2	2	2	2	2	2	2	7	7	14	14
Prior/ Concomitant Medications/ Procedures/ Hospitalizations	From signing ICF and until 90 days after the last dose of durvalumab or 28 days after the last dose of any other IP																														
Physical examination	X	X[a]	X	X	X	X	X	X	X	X	X	-	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	-	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	X	X	-
Vital signs	X	X	X	X	X	X	X	X	X	X	X	-	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	X	X	-
Hematology laboratory	X	X[b]	X	X	X	X	X	X	X	X	X	-	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry laboratory	X	X[b]	X	X	X	X	X	X	X	X	X	-	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X
Requalification Criteria	-	-	-	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Coagulation	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	X	-	-	-
Urinalysis	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-
Quantitative immunoglobulins	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	X	-	-	-
Thyroid function tests	X	X	-	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	-	-	-
Constitutional symptoms	X	X	-	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	-	-	-
Tumor Lysis prophylaxis	-	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PREGNANCY																															
Pregnancy Testing - All FCBP	X	X	X[c]	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	X	X	-
Lenalidomide Counseling - All FCBP (up to COO identification and stratification)	X	X	-	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Schedule of Assessments (Continued)

EVENTS	Screening	INDUCTION																CONSOLIDATION									EOT (PD)	Safety FU		Efficacy FU[j]
Cycle		1			2		3		4		5		6		7		8	EOI 1	2	3	4	5	6	7	8	9				90d up to 2 years from C1D1
Planned Day	-28 to-1	1	8	15	1	15	1	15	1	15	1	15	1	15	1	15	1	15	1	1	1	1	1	1	1	1	1	IP +28d	Dur +90d	
Window (± day)		2	1	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	7	2	2	2	2	2	2	2	2	7	7	14	14
Arm B Pregnancy Testing - for FCBP with Regular or No Menstrual Cycles	X[d]	Weekly during first 28 days; every cycle on Day 1 thereafter																End of lenalidomide and 28 days after the last dose of lenalidomide												
Arm B Pregnancy Testing - for FCBP with Irregular Menstrual Cycles	X[d]	Weekly during first 28 days; every cycle on Days 1 and 14 thereafter																End of lenalidomide and 14 and 28 days after the last dose of lenalidomide												
Birth Control	up to 12 months after the last dose of rituximab																													
BIOMARKERS																														
Tumor Biopsy	X	-	-	-	X[e]		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X[f]	-	-	-
Submit Lymph Node / Tumor Biopsy to Central Laboratory	X	-	-	-	X		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-
Saliva Samples for Biomarkers	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PBMC isolation for biomarkers	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	-	-	-	X	-	-	-
Whole blood biomarker for immunophenotyping	X	X	X	X	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum samples for biomarkers (ie sPD-L1)	X	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-
Plasma samples (cytokines/ soluble factors; circulating tumor DNA)	X	X	X	X	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-
EFFICACY ASSESSMENTS																														
FDG-PET scan[g]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	X	-	-	-

Table 3: Schedule of Assessments (Continued)

EVENTS	Screening	INDUCTION																CONSOLIDATION									EOT (PD)	Safety FU		Efficacy FU [j]
Cycle		1			2		3		4		5		6		7		8		EOI 1	2	3	4	5	6	7	8	9				
Planned Day	-28 to-1	1	8	15	1	15	1	15	1	15	1	15	1	15	1	15	1	15	1	1	1	1	1	1	1	1	1		IP +28d	Dur +90d	90d up to 2 years from C1D1
Window (± day)		2	1	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	7	2	2	2	2	2	2	2	2	7	7	14	14
CT Scan (neck, chest, abdomen and pelvis)	X	-	-	-	-	-	-	X[h]	-	X[h]	-	-	-	-	-	-	-	-	X	Every 3 months (± 1 week) up to PD								X	Every 3 months (± 1 week) up to PD		
Response Assessment (Cheson, 2014)	-	-	-	-	-	-	-	X[h]	-	X[h]	-	-	-	-	-	-	-	-	X	Every 3 months (± 1 week) up to PD								X	Every 3 months (± 1 week) up to PD		
Bone marrow biopsy and aspirate	X[i]	Within 28 days of a suspected CR, except in subjects with no evidence of lymphomatous marrow involvement at baseline																											-	-	-
Progression and Survival follow-up	for up to 5 years after the last subject is enrolled																														
Subsequent Anti-lymphoma therapy	See Section 6.3.2 for more details																														
PHARMACOKINETICS																															
PK analysis	-	X	X	X	X	X	-	-	X	X	-	-	X	-	-	-	X	-	X	X	X	X	X	X	-	X	-	X	-	-	-
Immunogenicity (ADA)	-	X	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	X	-	X	-	X	-	X	-	X	-	-	-
TREATMENT																															
Dispense Study Drug	-	X	-	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	-	-	-	-
Drug Accountability	-	-	-	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	-	-	-

ADA = anti-drug antibodies; C = cycle; CNS = central nervous system; COO = cell of origin; CR = complete response; CT = computed tomography; D = day; Dur = durvalumab; ECOG= Eastern Cooperative Oncology Group; EOI = end of induction; EOT = end of treatment (day of last durvalumab planned dosing); FCBP = female of child-bearing potential; FDG-PET = fluorodeoxyglucose-positron emission tomography; FU = Follow-up; HCV = hepatitis C virus; HBV = hepatitis B virus; HIV = Human Immunodeficiency Virus; ICF = informed consent form; IP = investigational product; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PD-L1 = programmed cell death-ligand 1; PK = pharmacokinetics; SPM = second primary malignancy,

[a] If performed within 72 hours of Cycle 1 Day 1 examination do not need to be repeated at Cycle 1 Day 1.

[b] Safety laboratory assessments performed during Screening within 7 days of the first study treatment will not need to be repeated for Cycle 1 Day 1.

[c] Once during day -10 to -14, and within 24h prior to first lenalidomide dose.

[d] Once during day -10 to -14, and within 24h prior to C1D1, see Section 6 for more details.

[e] Either at C2D14 (± 7 days), C3D14 (± 7 days).
[f] PD ± 14 days.
[g] Imaging by FDG-PET scan will be performed also following a CR, see Section 6.4.3 for more details.
[h] Every 3 months (± 1 week). Or after 50% of induction treatment (between C3D15 and C4D1 for 6×R-CHOP; between C4D15 and C5D1 for 8×R-CHOP). See Section 6.4.2 for more details.
[i] ± 12weeks. Not necessary if PET (-), see Section 6.4.4 for more details.
[j] Following completion or discontinuation of durvalumab therapy per protocol for all subjects and completion of the last durvalumab subject's 90-day Safety Follow-up Visit (data cutoff date 06 Jun 2019), subjects are no longer required to be followed for disease progression, subsequent anti-lymphoma therapy, and overall survival.

6. PROCEDURES

After the US FDA Partial Clinical Hold, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R CHOP) after Cycle 1 regardless of DLBCL COO subtype. Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinued. This study continued enrollment into treatment Arm A. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, could continue study treatment after being reconsented.

Any questions regarding the protocol should be directed to the Celgene Medical Monitor or designee.

In the procedures section, assessments performed on C1D1 will always refer to the start of the initial R-CHOP treatment. For instances when C1D1 is in reference to the start of the consolidation drug treatment, this will be explicitly stated.

The Informed consent must be obtained prior to beginning any study 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 Celgene 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 anti-lymphoma therapy and disease progression or death.
- Withdraw consent for study treatment and Follow-up Period assessments, but allow data collection on subsequent anti-lymphoma therapy and death.
- Withdraw all consent.

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days of first dose of study induction treatment (C1D1) unless otherwise noted. Screen failed subjects may be re-screened under exceptional circumstances and will be subject to the Medical Monitor agreement.

Inclusion/exclusion criteria must be reviewed prior to treatment assignment. Waivers to the protocol will not be granted during the conduct of this study under any circumstances. The following will be performed at Screening as specified in the Table of Events (Table 3), initiating once the informed consent has been obtained:

- **Inclusion/Exclusion criteria** will be evaluated for subject eligibility during the 28 day Screening period.
- **Disease history** of DLBCL will include specific information regarding diagnosis, staging and histology, and grade.

- **Prior cancer therapies:** All subjects will be evaluated for any prior cancer treatments that may have been received. Any treatments related to DLBCL will result in exclusion from the study.
- **Complete medical history** will be obtained by the Investigator or qualified designee. 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 (including HIV and HCV infection) findings will be recorded within the source document and the case report form (CRF). Medical and medication history will be assessed in relation to the eligibility criteria as listed in Section 4.2.
- **Demographics** will include date of birth or age, sex, race, and ethnicity (if allowed by local regulations).
- **Prior and concomitant medications and procedures** will include all medications and procedures including transfused blood products (packed red blood cells, platelets, etc.), occurring ≤ 28 days before Screening and ongoing during Screening.
- **Bone Marrow Biopsy and aspirate** will be performed within 12 weeks prior C1D1.

  Note: If the screening FDG-PET demonstrates the bone marrow to be FDG-negative, no bone marrow biopsy (BMB)/aspirate is required.
- **ECOG Performance Status** (Oken, 1982) will be scored according to Appendix C.
- **Physical examination** including evaluation of lymph nodes, spleen, liver, heart, lung, abdomen, neurological status, and skin will be performed. Physical examination performed within 72 hours of C1D1 do not need to be repeated at C1D1.
- **Vital signs** will include height (Screening only), weight, body surface area (BSA), blood pressure, pulse, pulse oximetry, and body temperature.
- **Safety laboratory analyses** will be performed at a designated Central Laboratory, according to the Schedule of Assessments (Table 3). Central laboratory results must be used during Screening to evaluate subject eligibility, and may be repeated within the Screening window, if necessary. However, if for any reason Screening central laboratory results become unavailable following collection of the samples (eg hemolyzed samples), local laboratory results may be used after discussion with and approval of the Celgene Medical Monitor. Safety laboratory assessments performed during Screening within 7 days of the first study treatment will not need to be repeated for C1D1. Refer to the Laboratory Manual for sample handling, storage, and shipment instructions.
  - **Hematology laboratories:** Complete blood count (CBC) with absolute differential will include hematocrit, hemoglobin, white blood cell count (WBC) with differential, and platelet count.
  - **Serum chemistry laboratories**: will include albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), amylase, aspartate transaminase (AST/SGOT), bilirubin, calcium, chloride, creatinine, gamma glutamyl

transferase, glucose, lactic acid dehydrogenase (LDH), lipase, phosphorous, potassium, sodium, total protein, serum urea/blood urea nitrogen (BUN), and uric acid.

Calculated creatinine clearance (CrCl) will be estimated by central laboratory using the Cockcroft-Gault formula:
CrCl (mL/min) = ((140 – age) (weight [kg])) / (72 (serum creatinine [mg/dL])); for females, the formula is multiplied by 0.85 (Cockcroft, 1976).
Alternatively, the CrCl can be calculated with a 24-hour urine collection.

- **Coagulation tests** will include prothrombin time, international normalized ratio (INR) and partial thromboplastin time (PTT or activated PTT).
- **Urinalysis** (a urine dipstick may be used). The urinalysis will include color, appearance, specific gravity, pH, glucose, ketones, blood, bilirubin, and protein. A microscopic examination will be performed if urinalysis result is abnormal. Additional urinalyses will be performed as considered clinically necessary.

- A **Tumor Biopsy** will be required of all subjects during Screening. Please refer to Section 6.8 for details.
  - Local Pathology review: Anonymized reports should be submitted, as well as locally stained slides.
  - Gene expression profile (GEP) analysis to determine COO will be performed on all subjects. Genomic subtype analysis is not necessary for determination of eligibility but must be performed prior to the start of Cycle 2 for each subject.
  - Tumor biopsies will also be used for other biomarker analysis as described in Section 6.8.
- **Biomarker saliva and blood sample(s):** Saliva and blood samples will be collected at Screening for pharmacogenomics and Pd analyses as outlined in the Biomarker Collection Schedule (Table 3) and Section 6.8.
- **Quantitative immunoglobulins** including IgG, IgA, and IgM will be measured.
- **Hepatitis B virus (HBV) testing (**assessed locally**)** 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). For subjects with previous HBV infection which is inactive at the time of Screening, viral DNA levels may be measured (see Section 4.3, Number 7).
- **Thyroid function tests:** Assessments of thyroid stimulating hormone (TSH), fT4, and fT3 will be performed.
- **Central nervous system (CNS) lymphoma evaluation and CNS prophylaxis:** CNS evaluation will be performed in selected patients to be at high risk for CNS involvement by lymphoma. Central nervous system involvement should be ruled out if any of the following involvement or criteria are observed: paranasal sinus, testicular, epidural, bone marrow, kidney or adrenal gland, DLBCL, concurrent expression of MYC and BCL-2 protein (ie, double expressing lymphoma [DEL]),

double hit lymphoma (DHL)/ triple hit lymphoma (THL) by FISH/cytogenetics analysis, or ≥2 extranodal sites and elevated LDH. If a subject has evidence of CNS disease on evaluation of spinal fluid and /or neuroimaging studies (performed if a subject has any review of symptoms and / or neurological findings suspicious for CNS involvement), the subject would be excluded from enrolling in this study.

  - In addition to routine CSF evaluation, flow cytometric analysis to rule out lymphomatous involvement is required.
  - Subjects at high-risk for developing secondary CNS disease (as described above) must also receive prophylactic chemotherapy according to NCCN guidelines or institutional standards. Refer to Section 8.3.2 for required and permitted concomitant CNS prophylaxis treatment.

- **Echocardiogram (2-D ECHO) or multi gated acquisition scan (MUGA)** for assessment of LVEF. The MUGA is the preferred method for LVEF evaluation over the use of an ECHO.
- 12-lead **Electrocardiogram (ECG)** will be performed to assess heart electrical function. If an ECG was performed as standard of care within 28 days of dosing, those data may be used to fulfill the eligibility requirement.
- **Pregnancy testing** is applicable to all subjects who are females of childbearing potential. For FCBP, 2 pregnancy tests must be performed (medically supervised; urine tests are provided and are the preferred method; if other test method [blood] is used, the minimum sensitivity required is 25 mIU/mL): (1) one during Screening Period (between Day- 10 and -14) and (2) one within 24 hours prior to the start of lenalidomide (refer also Section 6.2 for FCBP with COO unknown at C1D1). Negative results are required for IP administration. Please refer to the Pregnancy Prevention Plan located in Appendix E for further details.
- **Lenalidomide Counseling** about pregnancy precautions and the potential risks of fetal exposure to lenalidomide MUST be conducted for all subjects assigned to receive lenalidomide (Treatment Arm B) prior to receiving any IP. During counseling, subjects must be reminded to not share study drug and to not donate blood. Please consult the Lenalidomide Pregnancy Prevention Risk Management Plan (Appendix E) for details.
- **Constitutional symptom review** includes assessing subject for the presence of documentation B-symptoms (fever, weight loss, and night sweats).
- **Tumor Evaluation:** Integrated FDG-PET/CT is preferred for response assessment. The imaging modality (the same imaging modality [eg CT, MRI] and technique [eg the use of contrast, slice thickness for scans]) used at Screening should be used consistently throughout the study for all further assessments.
  - **Imaging by Computed Tomography (CT) scan**: All subjects are required to undergo a CT scan, with contrast, of the neck, chest, abdomen and pelvis during Screening. Tumor evaluations performed as part of the standard of care up to 28 days prior to C1D1 can be accepted as the baseline tumor evaluation. See Section 6.4.1 for further details.

  - **Imaging by FDG-PET:** All subjects are required to undergo a FDG-PET scan during Screening. See Section 6.4.1 for further details.

- The assessment period for **Adverse Events (AEs) and SPMs** begins when the subject signs the informed consent form. See Section 10 for further details.
- **Pre-specify Post-Induction Radiotherapy** if applicable. If the Investigator intends to administer radiotherapy post-induction (Section 7.2.2), this must be specified prior to enrollment of the subject through the Integrated Response Technology (IRT).

6.2. Treatment Period

Subjects will begin treatment following the confirmation of eligibility. Treatment will start on C1D1 and must start within 28 days of signing the informed consent form (ICF). For all subsequent visits, an administrative window of ± 2 days for Day 1 visits of each cycle and ± 1 day for scheduled interim study visits (eg Cycle Day 8 and Day 15 visits) are allowed unless otherwise noted.

The treatment period referred to in this section includes both the induction and the consolidation study drug treatments. Treatment cycles are 21 days in length during the induction treatment period and 28 days in length during the consolidation treatment period and will occur as described in Section 7.2.

Study visits and subject assessments will be performed at the frequency specified in the Schedule of Assessments (Table 3). Scheduled assessments should be performed prior to dosing on the scheduled visit day, unless otherwise specified (ie, PK, Pd).

Unscheduled assessments may be performed as clinically indicated, and those visits should be recorded in the subject's source documents and CRF.

The following evaluations will be performed as specified in the Table of Events (Table 3):

- **Concomitant Medications and Procedures** will be collected from signing of informed consent through 90 days after the last dose of durvalumab or 28 days after the last dose of any other IP, whichever is later. This will include all recent and current medications and procedures, including transfused blood products (packed red blood cells, platelets, etc.).
- **Bone Marrow Biopsy and aspirate** will be performed to confirm a CR (within 28 days for confirmation of a suspected CR), except in subjects with no evidence of lymphomatous marrow involvement performed during Screening.

  Note: If a FDG-PET-CT is performed and confirms FDG-negative CR, no bone marrow biopsy (BMB)/aspirate is required.
- **ECOG Performance Status** will be performed on Day 1 of each cycle and scored according to Appendix C.
- **Physical examination:** Documentation of any enlargement of the lymph nodes, spleen and/or liver should be recorded in the source document and CRF.
- **Vital signs**

- **Safety laboratory tests** (Hematology and Serum Chemistry) will be performed at the designated central laboratory during Day 1 of every cycle, weekly during cycle 1 (Days 1, 8 and 15), at Day 15 of Cycles 1-4 during the induction treatment and EOT.
- An **On-treatment Tumor Biopsy** is required when clinically feasible during Cycle 2 (C2D14 ±7 days) or during Cycle 3 (C3D14 ±7 days). The collection of tumor tissue is also required for all subjects at the time of disease progression following an objective response (PR or CR). See Section 6.8.1.
- **Thyroid function tests:** on Day 1 of each treatment cycle.
- **Pregnancy test** is required for all FCBP on Day 1 of each treatment cycle. See also Appendix E for details.
  - For all FCBP for whom COO results are pending and or determined as ABC before C1D8, and to respect the pre-lenalidomide dosing rules (explained in Section 6.1: one test between Day -10 and -14 and one test within 24 hours prior to the start of lenalidomide) a test must be performed, for example on C1D8 (or between Day -10 and -14 from C2D1) and within 24 hours prior C2D1.
  - FCBP in Arm B with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.
  - FCBP in arm B with irregular menstrual cycles must agree to have pregnancy tests between Day -10 and -14 prior to the start of lenalidomide, weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
- **Lenalidomide Counseling** will be conducted on Day 1 of each treatment cycle during the induction treatment period, and at end of induction (EOI) for all subjects assigned to receive treatment with lenalidomide (Treatment Arm B). See Appendix E for details.
- **Constitutional Symptom Review** on Day 1 of each treatment cycle.
- **Tumor Evaluation:** Integrated FDG-PET/CT is preferred for response assessment. The imaging modality (the same imaging modality [eg CT, MRI] and technique [eg the use of contrast, slice thickness for scans]) used at Screening should be used consistently throughout the study for all further assessments.
  - **Imaging by CT scan**: All subjects are required to undergo a CT scan, with contrast, of the neck, chest, abdomen and pelvis every 3 months (±1 week) for the first 2 years. During induction treatment, it is acceptable to perform the scans at 12 week intervals. It is also acceptable to perform the scans after 50% of induction treatment (between C3D15 and C4D1 for 6xR-CHOP schedule; between C4D15 and C5D1 for 8xR-CHOP schedule). See Section 6.4.1 for further details.

  - **Imaging by FDG-PET** will be performed following a CR. Further evaluation by FDG-PET scans are optional, except PET scan at the end of induction, and may be performed according to the scheduled CT scans to align with the efficacy response. See Section 6.4.1 for further details.

- **Efficacy Response** will be assessed locally along with the CT scan schedule until PD or premature discontinuation from the study and documented in the CRFs based on the 2014 International Working Group Response Criteria for Non-Hodgkin's Lymphoma (Cheson, 2014) according to the Schedule of Assessments (Table 3).
- **Pharmacokinetic Analysis** will be performed on blood samples collected according to the schedule described in Section 6.6.
- **Biomarker blood sample(s):** Samples for biomarker analyses will be collected as outlined in the Schedule of Assessments (Table 3) and Section 6.8.
- **Immunogenicity blood samples** will be collected as outlined in Section 6.7.
- **Study Drug Administration and Accountability:** Study drug will be administered at the Day 1 visit of each cycle. Intravenous treatments will be administered at the clinic and oral drugs will be provided to the subject for treatment as prescribed. Starting C2D1, study drug accountability will be performed and treatment compliance assessed.
- **Adverse events and SPMs** (refer to Section 10).

6.2.1. End of Induction Treatment (EOI)

Assessments will be performed at the end of the induction treatment period according to the Schedule of Assessments (Table 3) once a subject has completed or prematurely discontinued the induction treatment period. For subjects continuing on to the consolidation phase, the end of the induction treatment will initiate the start of consolidation treatment, therefore the end of induction visit will coincide with the first cycle visit (C1D1) for the consolidation treatment period.

In instances where the subject has prematurely discontinued from study treatment, the end of induction treatment will correspond with the end of study treatment (EOT) and only the EOT visits assessments will be performed

- **Concomitant Medications and Procedures**
- **Bone Marrow Biopsy and Aspirate** as necessary (see Section 6.4.4)
- **ECOG Performance Status**
- **Physical examination**
- **Vital signs**
- **Safety Laboratories:** Hematology, Serum Chemistry, and coagulation tests.
- **Quantitative Immunoglobins**
- **Thyroid Function Tests**

- A **2D-ECHO or MUGA**
- A **12-Lead ECG**
- **Pregnancy testing** is required for all FCBP.
- **Lenalidomide Counseling** for all subjects assigned to receive treatment with lenalidomide (Treatment Arm B). See Appendix E for details.
- **Constitutional Symptoms**
- **Tumor Evaluations:**
  - **Imaging by CT scan**: All subjects completing the induction treatment regimen should have a CT scan at the end of the induction treatment:
    - For subjects treated with 8 cycles of induction therapy, the end of induction CT scan should be done 6 months after C1D1.
    - For subjects treated with 6 cycles of induction therapy, the end of induction CT scan can be done before 6 months after C1D1, however, the subsequent CT scan should be performed at 9 months from C1D1. See Section 6.4.1 for further details.
  - **Imaging by FDG-PET** will be performed at the end of the induction treatment, but before the start of the consolidation treatment. See Section 6.4.1 for further details.
- Assessment of **Efficacy Response** and decision to continue in consolidation phase (see Section 7.2.3.1).
- **Pharmacokinetic Analysis** will be performed on blood samples collected according to the schedule described in Section 6.6. Collection of blood samples for PK analysis will be performed at the end of induction treatment for all subjects.
- **Biomarker blood sample(s):** Blood samples for biomarker analyses will be collected as outlined in the Schedule of Assessments (Table 3) and Section 6.8.
- **Study drug administration and accountability**
- **Adverse Events and SPMs** (refer to Section 10)

6.2.2. End of Treatment

An end of treatment (EOT) evaluation will be performed for subjects who completed the study treatment (the day of last durvalumab planned dosing) or who were withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue the subject from study treatment is made.

The following evaluations will be performed as specified in the Table of Events (Table 3):

- **Concomitant medications and procedures** will continue to be collected at EOT visit and through 90 days after the last dose of durvalumab or 28 days after the last dose of any other IP, whichever is later.
- **ECOG performance status**

- **Physical examination**
- **Vital signs**
- **Safety laboratory tests:** Hematology, Serum Chemistry, coagulation and urinalysis.
- A post treatment **Tumor Biopsy** will be required at the time of disease progression (within 14 days) from subjects who previously achieved an objective response (CR/PR). For subjects who have experienced disease progression without experiencing an objective response, a tumor biopsy at discontinuation is optional.
- **Quantitative immunoglobulins**
- **Thyroid function tests**
- A **2-D ECHO or MUGA**
- A **12-Lead ECG**
- **Pregnancy testing** is required for all FCBP at the EOT visit. All FCBP in Arm B, *with regular or no menstrual cycles* must have pregnancy tests at treatment discontinuation and at Day 28 following lenalidomide discontinuation. *If menstrual cycles are irregular*, the pregnancy testing must occur at treatment discontinuation and at Days 14 and 28 following lenalidomide discontinuation. See Appendix E for details.
- **Constitutional symptom review**
- **Tumor Evaluations:** FDG-PET/CT
  - **Imaging by CT scan**
  - **Imaging by FDG-PET** will be performed unless a FDG-PET confirmed CR was previously documented in an earlier cycle.
- **Efficacy response**
- **Immunogenicity blood samples**
- **Pharmacokinetic Analysis** according to the schedule described in Section 6.6.
- **Biomarker blood sample(s):** Blood samples for biomarker analyses will be collected as outlined in the Schedule of Assessments (Table 3) and Section 6.8.
- **Study drug accountability:** All final accountability of study drugs will be performed at the EOT visit.
- **Adverse events and SPMs** (refer to Section 10)
- **Subsequent anti-lymphoma/anticancer treatments status**

6.3. Follow-up Period

6.3.1. Safety Follow-up

All subjects will have a safety follow-up visit at 28 days and 90 days after last dose of study treatment, whichever is later for AE reporting, as well as serious adverse events (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in Section 10.1.

The following evaluations will be performed as specified in the Table of Events (Table 3):

- **Concomitant medications and procedures** will continue to be collected through 90 days after the last dose of durvalumab or 28 days after the last dose of any other IP, whichever is later.
- **ECOG performance status**
- **Physical examination**
- **Vital signs**
- **Safety laboratory tests:** Hematology, Serum Chemistry.
- **Pregnancy testing** is required for all females of childbearing potential (FCBP). FCBP in Arm B *with regular or no menstrual cycles* must have pregnancy tests at treatment discontinuation and at Day 28 following lenalidomide discontinuation. *If menstrual cycles are irregular*, the pregnancy testing must occur at treatment discontinuation and at Days 14 and 28 following lenalidomide discontinuation. Pregnancy tests will be performed for all FCBP 90 days after the last dose of durvalumab.
- **Adverse events including SPMs** will be assessed up to 90 days after last dose of durvalumab. Adverse events will be graded according to the NCI-CTCAE version 4.03 unless otherwise specified in this document. Subjects treated with lenalidomide during any stage of the study will continued to be followed for SPM for up to 5 years after enrollment (C1D1) of the last subject to receive lenalidomide as part of their study treatment.

6.3.2. Efficacy Follow-up

The Follow-up Period begins once all study treatments have been discontinued or have completed the full course of treatment as per protocol and contact or visits will be performed every 90 days (±14 days) post last dose of study treatment until disease progression. This includes subjects who discontinue treatment due to toxicity, as well as those who discontinue before progression to receive a new anti-lymphoma therapy.

Subjects will be followed for disease progression, and subsequent anti-lymphoma treatments. Efficacy assessments will continue at the protocol specified time points until disease progression, withdrawal of consent, or the initiation of a subsequent anti-lymphoma treatment.

In addition, physical examination for lymphadenopathy and organomegaly, and CBC with differential and serum chemistry including LDH test, will be repeated at the same time with the

efficacy assessments according to the schedule described in Table 3 up to two years after C1D1. Survival status of the subject will be documented and for deceased subjects, the date and cause of death will be documented in the CRFs, when available.

Following the documented disease progression, subjects will be followed for subsequent anti-lymphoma therapy every 6 months (±1 month) until withdrawal of ICF, or up to 24 months from the subject's last durvalumab dose, by contact with the subject or subject's caregiver.

6.3.3. Follow-up for Progression or Long-term Follow-up

After the end of treatment visit, all subjects will continue to be followed for disease progression for up to 5 years after the last subject is enrolled (C1D1) or until death, lost to follow-up, consent withdrawal, or the End of Study whichever occurs first according to the Table 3. Subsequent anti-lymphoma therapies should be collected at the same time schedule.

Following completion or discontinuation of durvalumab treatment per protocol for all subjects, and completion of last durvalumab subject's 90-day Safety Follow-up Visit (data cutoff date 06 Jun 2019), subjects are no longer required to be followed for disease progression, subsequent anti-lymphoma therapy, and overall survival. Follow-up procedures, efficacy assessments, central labs, imaging, AEs/SAEs and survival data will no longer be collected in the case report forms (CRFs).

6.4. Efficacy Assessment

Efficacy response assessments will be performed throughout the study treatment period and during the follow-up period for subjects until they have discontinued the treatment for disease progression or withdrawn consent from the study for further evaluation. Efficacy response assessment for this study will be based on the 2014 IWG Response Criteria for lymphoma (Cheson, 2014; Appendix B).

Tumor assessments will be performed by the Investigator. There is no central radiology review in this clinical study. However, tumor assessment data including images should be made available to the Celgene Medical Monitor or designee upon request. Once a subject has experienced confirmed progression, no further scans are required.

6.4.1. Efficacy Assessments

Integrated FDG-PET/CT is preferred for response assessment, however, CT scans are required for all tumor assessment and FDG-PET scans are required at Screening and for confirmation of CR. The imaging modality (eg CT, MRI and technique for example, use of contrast, slice thickness for scans) used at Screening should be used consistently throughout the study for all further assessments.

Scans previously acquired as standard of care within 28 days prior to C1D1 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.

6.4.2. Imaging by CT Scans

Subjects are required to undergo contrast-enhanced CT scan of the neck, chest, abdomen and pelvis as the required imaging modality for this study. An integrated FDG-PET/CT is the preferred modality. Imaging by CT scan without contrast or magnetic resonance imaging (MRI) 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.

Computed tomography scans will be performed until disease progression at the following intervals:

- Screening (within 28 days of C1D1).
- Every 3 months (± 1 week) starting C1D1 for the first 2 years.

Note: During induction treatment, it is acceptable to perform the scans at 12 week intervals to align with the treatment cycles

- During induction treatment, it is also acceptable to perform the scans as described below:
  - Interim Staging after 50% of induction therapy was administered
    - For subjects treated with **8 cycles** of R(2)-CHOP: between C4D15 and C5D1
    - For subjects treated with **6 cycles** of R(2)-CHOP: between C3D15 and C4D1
  - Final Staging (EOI) after 100% of induction therapy was administered
    - For subjects treated with **8 cycles** of R(2)-CHOP: after C8D15
    - For subjects treated with **6 cycles** of R(2)-CHOP: after C6D15

Note: the next CT scan after EOI should be performed at 9 months, independently of the number of cycles in induction, then every 3 months until 2 years after C1D1.

Following completion of treatment or discontinuation of treatment for any reason other than disease progression, the CT scan assessment will continue until disease progression, subsequent anti-lymphoma treatment or withdrawal of consent in the Follow-up period based on the schedule above. Unscheduled tests may be ordered at any time as clinically indicated.

After 2 years, CT scans are no longer required per protocol, however assessments may be continued according to local clinical practice.

Following completion of the last durvalumab subject's 90-day safety follow-up (data cutoff date 06 Jun 2019) and discontinuation of the Follow-up Period, the CT scan assessments are no longer required to be performed and collected in the CRFs.

6.4.3. Imaging by FDG-PET Scans

A FDG-PET scan (either as part of the integrated PET/CT or as a separate scan) using 18F-fluorodeoxyglucose (18F-FDG) is required of all subjects at Screening. Follow-up scans will be performed to confirm a CR. A FDG-PET is to be performed at the end of the induction treatment, but before the start of the consolidation treatment.

Confirmation of a CR during the induction period will be performed on Day 1 of the following cycle prior to the subsequent study treatment. This FDG-PET confirmatory scan is acceptable if performed up to 3 days prior to next treatment. Further evaluation by PET scans are optional and may be performed according to the scheduled CT scans to align with the efficacy response.

A FDG-PET scan is to be performed at the following intervals:

- During Screening for a baseline image (within 28 days of C1D1).
- Any time during the study treatment (within 14 days following demonstration of CR by CT scan alone) to confirm CR.
- End of induction treatment unless a FDG-PET-confirmed CR was previously documented in an earlier cycle.
- End of treatment unless a FDG-PET-confirmed CR was previously documented in an earlier cycle.
- The FDG-PET scans are optional at all other response assessment time points.

A positive FDG-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 (Appendix B).

A dedicated contrast-enhanced CT scan may be required in addition to the FDG-PET 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.

6.4.4. Bone Marrow Biopsy and Aspirate

Bone marrow biopsy (BMB) and aspirate (BMA) will be performed for diagnosis and efficacy assessments at:

- Screening

  Note: if a bone marrow sample was collected within 12 weeks of C1D1, that sample can be used.

- Within 28 days of a suspected CR. This sample is necessary for confirmation of the CR, except in subjects with no evidence of lymphomatous marrow involvement performed during Screening.

  Note: If an FDG-PET is performed and confirms FDG-negative CR, no BMB/aspirate is required to confirm CR.

Neither BMB nor BMA samples are acceptable for the confirmation of the diagnosis or the determination of COO by the NanoString assay and should not be submitted to the Central Laboratory.

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; coagulation; serum immunoglobulins;

concomitant medications and procedures; pregnancy testing (for FCBP only); cardiac function and ECG.

Safety assessments will be performed during Screening and will be repeated weekly during Cycle 1, bi-weekly during Cycles 2 through 4, and once every 3 weeks during the induction treatment period and once every 4 weeks during the consolidation treatment period.

The assessment period for AEs begins when the subject signs the ICF. Adverse Events (including SPMs) will be assessed throughout the study until 90 days after the last dose of durvalumab or 28 days after the last dose of any other IP, whichever is later. Subjects treated with lenalidomide during any stage of the study will continued to be followed for SPM for up to 5 years after enrollment (C1D1) of the last subject to receive lenalidomide as part of their study treatment.

Adverse events will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 unless otherwise specified in this document.

Tumor flare reaction (pseudoprogression) will be graded according to NCI-CTCAE version 3.0 (Table 9).

Tumor lysis syndrome will be assessed according to the Cairo-Bishop index (Appendix D).

Definitions for AEs and SAEs are found in Section 10.

6.5.1. Safety Run-in Stage

This study includes a *Safety Run-in Stage* to evaluate the safety of the treatment combinations until at least 10 subjects are included. Following Partial Clinical Hold instituted by the US FDA which affects Arm B, the *Safety Run-in Stage* will evaluate safety of the treatment Arm A combinations when at least 10 subjects have been included into Arm A and have been treated for at least one cycle of study treatment or discontinued prematurely.

The decision to continue enrollment into the *Expansion Stage* will occur at the discretion of the Sponsor following the evaluation of the *Safety Run-in Stage* by the SRC. This review will take place after at least 10 subjects have been enrolled into Arm A and have completed at least one cycle of study treatment or discontinued prematurely.

The *Expansion Stage* will start once study treatment is confirmed to be tolerable during the *Safety Run-in Stage*. Additional subjects up to the total sample size will be enrolled in the expansion phase to evaluate clinical activity as well as to further define the safety profile of the study treatments.

6.5.2. Safety Review Committee

A SRC will be convened to evaluate the safety profile and tolerability of the *Safety Run-in Stage* as well as potentially other safety data in this clinical study.

Following data review by the Sponsor and the SRC, it may be decided to proceed with only one treatment arm or to extend the Safety Run-in Stage with more subjects. Following Partial Clinical Hold instituted by the US FDA which affects Arm B, the *Safety Run-in Stage* will evaluate safety of the treatment Arm A combinations when at least 10 subjects have been

included into Arm A and have been treated for at least one cycle of study treatment or discontinued prematurely.

The SRC will continue to review safety data regularly throughout all phases of the study and make recommendations about study continuation and dose modifications for the IPs as appropriate. The SRC will also be informed about any relevant safety data available from other durvalumab studies.

The SRC membership will be comprised of Investigators who are participating in the study and who have sufficient experience in early phase clinical studies in lymphoma, as well as the Celgene Medical Monitor and Drug Safety Physician. Other study team members (eg study statistician, clinical research scientist or trial safety manager) may also participate in SRC meetings as needed.

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

6.6. Pharmacokinetics (PK)

Blood collections for pharmacokinetic analysis of durvalumab blood levels are mandatory and will be performed on all subjects enrolled according to the sample collection schedule as outlined below.

During PK sampling days, dosing and sample collection information including dosing date, dosing time (24-hour clock; eg, 2:00 pm = 1400), and actual PK blood sampling time (24-hour clock) should be accurately documented on the appropriate CRF pages. All the sampling timepoints are relative to the durvalumab treatment administration schedule. For subjects on Treatment Arm B, the first sample collection of any visit treatment during induction therapy should precede lenalidomide dosing for that day.

6.7. Immunogenicity

Blood samples for immunogenicity analysis will be collected from all subjects. Samples will be collected between 5 and 30 minutes prior to administration of durvalumab.

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 collected on Day 1 of Cycle 1 and Cycle 2, and then every second cycle (Day 1 of Cycles 4, 6 and 8 [if applicable] of induction treatment and Day 1 of cycles 2, 4, 6 and 8 of consolidation treatment) until the end of durvalumab treatment, and the EOT visit (−30 to −5 minutes prior to the very last dose of durvalumab).

6.8. Biomarkers, Pharmacodynamics and Pharmacogenomics

6.8.1. Tumor Tissue Biopsy

The collection of tumor tissue is mandatory.

Table 4: Tumor Tissue Biopsy Collection Time points for Biomarkers

Timepoints	Window	Requirement
Screening[a]		Mandatory
During Treatment	C2D14 (±7 days) or C3D14 (±7 days)	Required when clinically feasible
At time of PD in subjects who achieved a response (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)

CR = complete response, PD = progressive disease, PR = partial response

[a] It is required to submit Local Pathology reports (anonymized) associated with these tissue and diagnosis to Central Laboratory. For subjects with a poorly accessible tumor, an archival diagnostic lymph node/tumor FFPE biopsy sample, acquired by a surgical or core needle biopsy prior to signing the informed consent form, may be acceptable for enrollment.

Due to the required amount of tissue needed to perform the necessary analyses, tumor biopsies collected by tumor excision or incision are strongly preferred, however core needle biopsies (4 passages preferred) are acceptable if a surgical biopsy is not clinically feasible.

Other commonly used devices (eg, endoscopy forceps or grasp biopsy) are also acceptable provided they yield an equivalent amount of tumor tissue.

Material from a fine needle aspiration is not acceptable.

Tissue will be formalin fixed and submitted to the Central Laboratory in order to evaluate the tumor microenvironment as well as to identify predictive/Pd biomarkers.

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.

Note: Neither BMB nor BMA samples are acceptable for the confirmation of the diagnosis or the determination of COO by the NanoString assay and should not be submitted to the Central Laboratory.

Refer to the Laboratory Manual for a summary of tumor tissue specific assessments and material to be provided, sample collection and processing instructions.

6.8.2. Saliva and Blood Samples for Biomarker Assessments

Saliva, whole blood, and whole-blood derived sample specimens will be collected and analyzed to evaluate protein, nucleic acid and cellular biomarkers that relate to durvalumab, combination treatment and disease status according to the schedule presented in Table 3.

A saliva sample will be collected at Screening. Blood samples for biomarker analyses will be collected from all subjects to assess Pd, predictive, and/or disease-related markers. Biomarker blood samples will be collected during induction and consolidation treatments, according to the collection schedule described in Table 3. Samples are to be collected prior to treatment. Details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

6.8.3. Gene Expression Analysis/NanoString Technology

Gene expression profiling will be performed on NanoString's nCounter® Analysis System with formalin-fixed paraffin-embedded (FFPE) biopsy material obtained during screening to identify the COO subtype for each eligible subject. Bone marrow tumor specimens (BMB or BMA) are not acceptable for this analysis.

The NanoString LST assay, which is based on the NanoString 20-gene assay for cell of origin subtyping in DLBCL, will be used in this current study. The LST assay profiles FFPE tissue using the previously reported 20-gene Lymph2Cx algorithm on the nCounter Dx analysis platform.

The NanoString 20-gene assay was verified against the original COO model defined by Lenz (Lenz, 2008) using an independent cohort of 68 FFPE biopsies. In the validation cohort the assay was accurate and robust, with > 95% concordance of COO assignment between two independent laboratories (Scott, 2014b).

6.9. Subject Reported Outcomes or Quality of Life or Health Economics

Not applicable.

6.10. Assessments After Primary Endpoint Was Met

Once the study has sufficient events for analysis of the primary endpoint of PFS, subjects will continue to be followed for subsequent anti-lymphoma treatments, including responses, and for the occurrence of any SPM.

7. DESCRIPTION OF STUDY TREATMENTS

This Phase 2, two-arm, open-label study is designed to evaluate durvalumab in combination with R-CHOP or in combination with R2-CHOP followed by durvalumab consolidation therapy in previously untreated subjects with high-risk DLBCL.

Subjects meeting the study eligibility criteria receive one cycle of induction therapy of durvalumab in combination with R-CHOP. Based on their DLBCL Cell-of-Origin subtype (ABC versus non-ABC) as determined by the NanoString LST assay before start of Cycle 2, subjects will then be allocated to one of two treatment arms from Cycle 2 onwards (or the cycle following COO determination). As a result of the US FDA Partial Clinical Hold, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R CHOP) after Cycle 1 regardless of DLBCL COO subtype. Enrollment into Arm B (durvalumab in combination with R2-CHOP) was discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, could continue study treatment after being reconsented.

Induction treatment will be administered until disease progression, unacceptable toxicity or the completion of induction treatment (6 to 8 cycles). Subjects completing induction treatment and achieving a CR (or a PR, see details on Section 7.2.3.1) will receive consolidation therapy comprised of durvalumab monotherapy for up to a total of 12 months from C1D1.

7.1. Description of Investigational Product(s)

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

Required medications for neutropenia will be selected by the Investigator according to local practice and provided by the investigative site.

Recommended medications such as aspirin and allopurinol, if used, will be selected by the Investigator according to local practice and provided by the investigative site.

7.1.1. Durvalumab

Durvalumab will be supplied by Celgene in single use vials in single count cartons. Each 10R (10 mL) 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.

Site 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 to 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 contain a 14-day supply of lenalidomide. Lenalidomide should be stored in accordance to the product label.

For additional information on preparation and storage please refer to the Pharmacy Manual, the Summary of Product Characteristics, or the IB.

No newly enrolled subjects are to be treated with the combination of durvalumab, R-CHOP plus lenalidomide. Only those subjects currently enrolled and receiving clinical benefit, based on the discretion of the Investigator, are eligible to remain on treatment following reconsent.

7.1.3. Rituximab

Celgene will provide commercial supplies, for countries where rituximab is designated as investigational product, labeled appropriately for investigational use as per the regulations of the relevant country health authority. Subjects enrolled in countries where rituximab is not designated as investigational product, should obtain commercially available product through their local hospital pharmacy or licensed distributer.

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

- Rituximab IV standard infusion time
- Rituximab IV generics
- Rituximab Subcutaneous (1400 mg/11.7 mL fixed dose; Hoffman-La Roche, 2016; Lugtenburg, 2015)

The protocol does not allow the use of rituximab IV rapid infusion or other CD20 antibodies (eg obinutuzumab, ofatumumab).

Please refer to the locally approved rituximab label or Pharmacy Manual for preparation, administration, or storage information, as well as for further information on rituximab including warnings, precautions, contraindications, and guidance on pregnancy prevention.

7.1.4. Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

The CHOP treatment regimen, will be administered to all subjects as a combination chemotherapy treatment of the following drugs: cyclophosphamide, doxorubicin, vincristine and prednisone/prednisolone.

Celgene will provide commercial supplies, for countries where cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone are designated as investigational product, labeled

appropriately for investigational use as per the regulations of the relevant country health authority. For subjects enrolled in countries where cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone are not designated as investigational product, commercially available product should be obtained through a local hospital pharmacy or licensed distributer.

Please refer to the locally approved product/prescribing information, the Summary of Product Characteristics or the IB for further information on cyclophosphamide, doxorubicin, vincristine and prednisone therapies including warning, precautions, and contraindications.

7.2. Treatment Administration and Schedule

Information regarding prohibited, required, or recommended prophylactic treatments can be found in Section 8.

7.2.1. Optional Pre-phase Treatment

Subjects with bulky disease (defined for this study as having one lesion with at least one diameter ≥ 7.0 cm), systemic symptoms, compressive disease, elevated bilirubin due to lymphoma, or rapidly progressing adenopathies may at the discretion of the Investigator receive pre-phase treatment with 100 mg/day prednisone, or equivalent, for a maximum of 7 days prior to beginning the Treatment Period.

A washout period is not required. Pre-phase treatment may be immediately followed by prednisone as part of R-CHOP, and then a corticosteroid taper is allowed. However, the Screening PET, CT, lymph node biopsy, and bone marrow biopsy (and if applicable, also the bone marrow aspirate) should be completed before initiating corticosteroids.

Pre-phase treatment with vincristine or any other chemotherapy is prohibited.

7.2.2. Pre-specify Post-Induction Radiotherapy

The Investigator may prospectively choose to give local radiotherapy after study chemotherapy for the treatment of a particular site of bulky disease or a large mass. In the case of consolidation treatment, bulky disease is defined as one lesion with at least one diameter ≥ 7.0 cm. However, the decision to treat and the location to be treated must be determined during the Screening Period, source documented, and registered in the IRT.

7.2.3. Study Drug Treatment[6]:

Subjects who are eligible to participate in this study will receive one cycle of induction therapy of durvalumab in combination with R-CHOP. Subjects will then be allocated to one of two treatment arms from Cycle 2 onwards (or the cycle following COO determination) based on their DLBCL COO subtype. Eligible subjects for whom the COO has already been identified as ABC

[6] As a result of the US FDA Partial Clinical Hold, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R CHOP) after Cycle 1 regardless of DLBCL COO subtype. Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, could continue study treatment after being reconsented.

subtype by NanoString LST assay before starting study treatment may have lenalidomide added starting with C1D1 onwards:

- **Arm A:**
  Durvalumab in combination with R-CHOP
- **Arm B[7]:**
  Durvalumab in combination with lenalidomide and R-CHOP

The induction period will last for either 6 or 8 cycles at the discretion of the treating Investigator, or until unacceptable toxicity, disease progression, or withdrawal of consent.

Subjects for whom COO determination is inconclusive will continue treatment in study Treatment Arm A. Subjects for whom the COO is determined as ABC only after Cycle 2 will be allocated to Arm B whenever the results become available, however, missed cycles will not be made up. After the US FDA Partial Clinical Hold enrollment of new subjects into Arm B has been discontinued. If receiving clinical benefit at the discretion of the Investigator, subjects may continue treatment in Arm B after being reconsented. Any newly enrolled subject with DLBCL of ABC COO subtype after the US FDA Partial Clinical Hold will continue induction therapy on Arm A after Cycle 1.

Subjects tolerating treatment and achieving a CR (or PR, see Section 7.2.3.1) will continue consolidation treatment up to a total of 12 months from C1D1 as follows:

- **Arm A+B:** Durvalumab monotherapy

More detailed information regarding the administration and schedule of the study treatments is found in the following sections.

Dosing Sequence:

The following sequence of study treatment administration should be followed for each induction treatment cycle:

1. Durvalumab: Day 1 of each cycle should start with the administration of IV durvalumab followed by a 2-hour observation period post infusion.
2. Subsequently, rituximab is administered. Rituximab administration may be split over 2 consecutive days according to local clinical practice. Rapid infusion of rituximab is not allowed in this clinical study.
3. This is followed by the administration of the CHOP chemotherapy.
4. This is followed by lenalidomide (Arm B only, ie from C2D1 onwards).

The method of administration, the dose and the timing of each study treatment drug is outlined below in Table 5.

[7] As a result of the US FDA Partial Clinical Hold, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R CHOP) after Cycle 1 regardless of DLBCL COO subtype. Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, could continue study treatment after being reconsented.

Table 5: Induction Treatment

Drug	Dose	Route of Administration	Dosing Days (21-day cycle)	Dosing sequence (Cycle Day 1)
Durvalumab	1125 mg	IV	1	1
Rituximab	375 mg/m^2	IV	1	2
Cyclophosphamide	750 mg/m^2	IV	1	3
Doxorubicin	50 mg/m^2	IV	1	
Vincristine	1.4 mg/m^2 (up to 2.0 mg total)	IV	1	
Prednisone / Prednisolone[a]	100 mg	IV/ PO	1-5	
Lenalidomide **From C2D1; Arm B only (discontinued enrollment of new subjects)**	15 mg	PO	1-14	4

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; IV = intravenous; PO = per os, oral administration.

[a] Prednisone/Prednisolone may be administered as an IV infusion or PO on Day 1 followed by PO administration on Days 2-5 of each cycle. Prednisone should be administered after lenalidomide dosing. For subjects on Treatment Arm A, prednisone may be given before the other drugs of the CHOP chemotherapy.

7.2.3.1. Criteria for stopping induction treatment and for starting consolidation treatment

During and at the end of the induction treatment, the Investigator may initiate new anti-lymphoma therapy if study treatment is discontinued because of an insufficient therapeutic response to the first-line induction therapy.

Subjects with a CR after the end of induction therapy will continue on consolidation treatment with durvalumab.

Subjects achieving a PR at the end of the induction treatment may be allowed to continue with consolidation therapy with durvalumab if the Investigator considers this to be clinically justified.

Subjects with a SD or PD after the end of induction therapy will discontinue the study treatment.

7.2.3.2. Durvalumab (MEDI4736)

Durvalumab will be administered to all subjects, initiating on C1D1 for 6 to 8 cycles of 21-days per cycle during the induction treatment at a fixed dose of 1125 mg as an IV infusion.

During the consolidation treatment stage, durvalumab will be administered to all subjects as an IV infusion at 1500 mg on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1 or until unacceptable toxicity, disease progression, or withdrawal of consent.

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

Durvalumab treatment should be administered on Day 1 of each cycle without any drug hold unless approved by the Celgene Medical Monitor.

Note: Special monitoring requirements are associated with each infusion of durvalumab, both during and after the infusion:

- *Subjects will have their temperature, blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):*
  - At the beginning of the infusion (at 0 minutes)
  - 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 (±5 minutes) after the infusion (ie, 90, 120, 150, and 180 minutes from the start of the infusion)
- *If the infusion takes longer than 60 minutes, then temperature, blood pressure and pulse measurements should be collected every 30 minutes (±5 minutes) and as described above or more frequently if clinically indicated.*

Dose modifications will be performed according to criteria found in Table 6, Table 7, Table 8, Table 9 and Table 10. The dose may also be interrupted for toxicities not listed in those tables according to the clinical judgment of the Investigator. Refer to the SmPC or the IB for further information including warning, precautions, and contraindications.

7.2.3.3. Lenalidomide

No new subjects are to be treated with the combination of durvalumab, R-CHOP plus lenalidomide. Only those subjects currently enrolled and receiving clinical benefit, based on the discretion of the Investigator, are eligible to remain on treatment following reconsent.

Lenalidomide treatment will be initiated for subjects allocated to Treatment Arm B during the induction treatment from Cycle 2 onwards (or the cycle following COO determination). Treatment will begin on C2D1 at a dose of 15 mg oral administration (PO) once daily for 14 days of 21-days per cycle for 6 to 8 cycles. Eligible subjects for whom the COO has already been identified as ABC subtype by NanoString LST assay before starting study treatment, may have lenalidomide added starting with C1D1 onwards.[8]

On Day 1 of every cycle, lenalidomide will be administered in the clinic after the administration of durvalumab and R-CHOP. For subsequent dosing days, subjects should be instructed to take lenalidomide at approximately the same time each day as the Day 1 dosing for that cycle. There

[8] As a result of the US FDA Partial Clinical Hold, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R CHOP) after Cycle 1 regardless of DLBCL COO subtype. Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinuedSubjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the Investigator, could continue study treatment after being reconsented.

is no requirement for taking lenalidomide with or without food, or with or without certain types of foods or liquids.

A 7-day rest period following the 14 days of dosing (Days 15-21 of each induction cycle) is mandatory. The rest period may be extended for toxicity as needed (Section 7.2.5.4).

If a subject misses a dose of lenalidomide and it is within 12 hours of their normal dosing time, the subject 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 a greater than or equal to (≥) 12-hour interval between the two doses will not cause considerable drug accumulation.

Dose modifications will be performed according to criteria found in Table 13. The dose may also be modified for toxicities not listed in those tables based on the clinical judgment of the Investigator. Once a dose is reduced, re-escalation is not permitted. Refer to the Summary of Product Characteristics or the IB for further information including warning, precautions, and contraindications.

7.2.3.4. Rituximab

Rituximab will be administered at 375 mg/m^2 BSA on Day 1 of each 21-day cycle for 6 to 8 cycles as part of the R-CHOP treatment regimen.

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

Furthermore, it is up to the discretion of the Pharmacist and Investigator whether BSA will be recalculated for each cycle of rituximab, or whether the BSA calculated prior to the first dose of rituximab will be used throughout the study. If BSA is 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 local approved rituximab prescribing guidelines. Rituximab administration may be split over 2 consecutive days according to local clinical practice. Rapid infusion of rituximab is not allowed in this clinical study. Refer to approved product/prescribing information, Summary of Product Characteristics or the IB for further information, including warning, precautions, and contraindications.

7.2.3.5. Cyclophosphamide

Cyclophosphamide will be administered at 750 mg/m^2 BSA on Day 1 of each 21-day cycle for 6 to 8 cycles as part of the R-CHOP treatment regimen.

The cyclophosphamide dose may not be modified. Preparation and infusion rate are according to the package insert and local practice.

Urotoxicity including hemorrhagic cystitis, pyelitis, ureteritis, and haematuria have been reported with cyclophosphamide therapy. Prior, during and immediately after the administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity. Adequate treatment with mesna and/or strong hydration to force diuresis can markedly reduce the frequency and severity of bladder toxicity. Please refer to the cyclophosphamide prescribing information, the Summary of Product Characteristics or the IB for further details.

7.2.3.6. Doxorubicin

Doxorubicin will be administered at 50 mg/m^2 BSA on Day 1 of each 21-day cycle for 6 to 8 cycles as part of the R-CHOP treatment regimen.

The doxorubicin dose may not be modified. No other anthracycline may be substituted for doxorubicin. Liposomal doxorubicin is not permitted. Preparation and infusion rate are according to the package insert and local practice. Refer to approved product/prescribing information, the Summary of Product Characteristics or the IB for further information including warning, precautions and contraindications.

7.2.3.7. Vincristine

Vincristine will be administered at 1.4 mg/m^2 BSA (recommended capping at 2 mg absolute dose) on Day 1 of each 21-day cycle for 6-8 cycles as part of the R-CHOP treatment regimen.

The vincristine dose may be modified according to Table 11 and Table 12. Preparation and infusion rate are according to the package insert and local practice. Refer to approved product/prescribing information, the Summary of Product Characteristics or the IB for further information including warning, precautions and contraindications.

7.2.3.8. Prednisone

The prednisone start dose is a flat 100 mg PO or intravenous (IV) dose. Subsequent doses may be reduced for medical reasons at Investigator discretion.

Subjects should be instructed to take prednisone in the morning on scheduled dosing days. For subjects on Treatment Arm A, prednisone may be given before the other drugs of the CHOP chemotherapy.

In countries where prednisone is not available it will be acceptable to substitute prednisolone on a 1:1 basis for prednisone. It is also acceptable to administer the prednisone or prednisolone by IV rather than PO on Day 1 of the cycle for convenience. Refer to approved product/prescribing information, the Summary of Product Characteristics or the IB for further information including warning, precautions and contraindications.

7.2.4. Required Criteria for Induction Treatment Cycles (Requalification Criteria)

All subjects who have met the Screening requirements and are not experiencing AEs requiring a dose hold or which the treating Investigator considers to compromise the safety of the study subject, are eligible to receive study treatment on C1D1.

Subsequent cycles with induction treatment may begin on the next scheduled Day 1 if all of the following Requalification Criteria are met:

- ANC ≥ 1,000 cells/mm³ (1.0 x 10^9/L), unless secondary to lymphoma bone marrow involvement per Investigator assessment.
- Platelet count ≥ 75000 cells/mm³ (75 x 10^9/L), unless secondary to lymphoma bone marrow involvement per Investigator assessment.
- All other toxicities have resolved to ≤ Grade 2.
- A 7-day rest period has elapsed following the last dose of lenalidomide.

7.2.5. Dose Modifications (Interruption/Reduction)

The guidelines for dose modifications and toxicity management are provided in the following sections. These guidelines prepared by the Sponsor are intended to assist the clinical judgment of Investigator in the appropriate medical management of these toxicities and should only be applied to those events related to the study treatments. Dose modifications must be recorded in the Study Drug Record case report form (CRF).

Dose modifications are permitted in any cycle for appropriate management of AEs. Dose reductions are allowed for lenalidomide and vincristine. No dose reductions are allowed for durvalumab or the other drugs of the R-CHOP regimen. Nonetheless, treatment may be interrupted or discontinued, or the infusion rate for any IV treatment may be changed at the discretion of the Investigator for severe infusion or allergic reactions, or other toxicities.

If the requalification criteria for subsequent treatments are not met (after the rest period has elapsed) on Day 1 of the new cycle, the subject will be evaluated every 7 days for 14 days.

If the requalification criteria are met within 14 days, lenalidomide may be resumed or the Investigator may continue treatment without lenalidomide, if clinically appropriate.

Dose interruptions lasting beyond 21 days (> one cycle) should be discussed with the Celgene Medical Monitor.

Toxicity delays due to any drugs included in the R-CHOP regimen are allowed up to a maximum of two 14-day delays over the 6 to 8 cycle treatment duration. Should a delay be required for any one of the R-CHOP drugs, then the R-CHOP treatment must be delayed, with the exception of vincristine as described below.

If the criteria for the next treatment cycle are adequately met, but the subject develops peripheral neuropathy due to vincristine (Table 11), the Investigator may choose to skip the vincristine for the current cycle and resume vincristine on the defined R-CHOP schedule at the start of the next cycle. In this case, the skipped vincristine dose is not made up. If the subject cannot tolerate the lowest level of vincristine, it is acceptable to continue with the study drug treatment without vincristine.

If the requalification criteria are fulfilled, but the subject develops toxicity as described due to toxicities attributed to lenalidomide, durvalumab and R-CHOP should continue during the lenalidomide dose hold. If the requalification criteria are fulfilled, but the subject develops toxicity as described due to toxicities attributed durvalumab, R-CHOP should continue during the durvalumab dose hold. There is no maximum delay limit for lenalidomide which may be resumed later if the treatment criteria are met. Skipped doses of lenalidomide may not be made up and rest periods must be observed.

Subjects can discontinue any of the treatment regimens (durvalumab, lenalidomide or R-CHOP), and remain on study until completion of the scheduled consolidation treatment according to the following guidelines:

- If subjects discontinue durvalumab treatment, they may continue to receive the complete regimen of either R-CHOP or R2-CHOP during induction treatment.
- If the lowest dose of lenalidomide is not tolerated the subject will discontinue lenalidomide treatment. Subjects can remain on other remaining treatments should lenalidomide be discontinued.
- If R-CHOP is discontinued, subjects may continue on durvalumab with or without lenalidomide until all scheduled treatments have been administered and then proceed into the durvalumab consolidation treatment.

Lenalidomide may be resumed once the requalification criteria are met; however, skipped doses of lenalidomide may not be made up, and the 7-day rest period requirement of each cycle must be observed.

Durvalumab treatment should be administered on Day 1 of each cycle without any drug hold unless discussed with and approved by the Celgene Medical Monitor.

Durvalumab and lenalidomide may be continued during the induction for the remaining protocol defined treatment period, if R-CHOP is discontinued, provided the above treatment criteria are otherwise met, and rest periods are observed.

7.2.5.1. General Dose Modification Guidelines

Subjects will be evaluated for AEs at each visit using the NCI-CTCAE version 4.03 as a guide for severity grading, with the exception of TLS which will be graded according to the Cairo-Bishop index which can be found in Appendix D (Cairo, 2004) and TFR which will be graded using NCI-CTCAE Version 3.0.

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 determined 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 Section 7.2.5.

7.2.5.2. Dose Modification Guidelines for Durvalumab

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune-mediated AEs (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, 2012). Subjects should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (eg infection or disease progression), an immune-mediated etiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy.

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 as described in Table 6, Table 8, Table 9, and Table 10.

In addition to the dose modifications shown in Table 6, Table 8, Table 9, and Table 10, 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-mediated.
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 immunosuppressive therapies 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 Celgene Medical Monitor.

Table 6: General Dose Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

<table>
<tr><th colspan="3">Immune-mediated Adverse Events – General Considerations</th></tr>
<tr><th></th><th>Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td rowspan="2">Immune-mediated Adverse Events (Overall Management For toxicities not noted below)</td><td>Drug administration modifications of study drug/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 study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/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 study drug/study regimen
• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing</td><td rowspan="2">It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table:
– 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, patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and 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 (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV 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 Sponsor's medical monitor, 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 to 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).</td></tr>
<tr><td>Grade 1 No dose modification
Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.
If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper.
Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/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 at ≤10 mg/day or equivalent</td></tr>
</table>

Table 6: General Dose Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events (Continued)

Immune-mediated Reactions		
	Dose Modifications	**Toxicity Management**
	Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	– More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the 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 jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.
	Grade 4 Permanently discontinue study drug/study regimen Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/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 study drug/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 study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus)	

AE = adverse event; CTC = Common Terminology Criteria; imAE = immune-mediated adverse event; IV = intravenous; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF-α = tumor necrosis factor-alpha

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (ILD)	Any Grade	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
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/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 study drug/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 study drug/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 1-2mg/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-α inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Note: It is 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 PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). [a]

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (ILD)			– Consider pulmonary and infectious disease consult – Consider as necessary discussing with the Sponsor's medical monitor
	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 study drug/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 Sponsor's medical monitor. Hospitalize the subject – Supportive Care (oxygen, etc.) – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF-α inhibitors (eg infliximab at 5 mg/kg every 2 weeks' dose) started *Note: rule out sepsis and refer to infliximab label for general guidance before using infliximab* – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). [a]
Diarrhea/ Colitis	Any Grade	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, etc.) – 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; analgesics may mask symptoms of perforation and peritonitis

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Diarrhea/ Colitis	Grade 1 (Diarrhea: stool frequency of < 4 over baseline per day) (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
	Grade 2 (Diarrhea: stool frequency of 4-6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/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 study drug/study 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 such as (infliximab at 5 mg/kg once every 2 weeks) [b] **Caution:** It is 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, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). [a]

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Diarrhea/ Colitis	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; (Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; (Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	Grade 3 Permanently discontinue study drug/study regimen. for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. Grade 4 Permanently discontinue study drug/study regimen.	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, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis**	Any Grade	General Guidance	– Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin – Evaluate for alternative etiologies (eg viral hepatitis, disease progression, concomitant medications)

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis** **PLEASE SEE section immediately below this section to find guidance for management of "Hepatitis (elevated LFTs)" in HCC patients**	Grade 1 (AST or ALT > ULN and <3.0 x ULN and/or TB > 1.5 x ULN and <3.0 x ULN)	No dose modification Upon worsening, 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 Study drug/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 study drug/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 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 workup 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 (mycophenolate mofetil) [b]. Discuss with Sponsor's medical monitor if mycophenolate mofetil is not available. **Infliximab should NOT be used** - Once 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]
	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 X ULN, or elevations in bilirubin ≤ 5X ULN - Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline	For Grade 3 or 4 AST or ALT and/or TB elevation: - Promptly initiate empiric IV methylprednisolone at 1-4 mg/kg/day or equivalent - If still no improvement within 3-5 days despite 1-4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with Sponsor's medical monitor if mycophenolate motefil is not available. **Infliximab should NOT be used**

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis** **PLEASE SEE section immediately below this section to find guidance for management of "Hepatitis (elevated LFTs)" in HCC patients**		– Resume study drug/study regimen if elevations downgrade ≤ Grade 1 or baseline within 14 days and after completion of steroid taper – Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days For elevations in transaminase > 8X ULN or elevations in bilirubin > 5X ULN, discontinue study drug/study regimen Permanently discontinue study drug/study regimen for any case meeting **Hy's law (ALT and/or AST > 3X ULN and bilirubin > 2X ULN criteria** without initial findings of cholestasis [ie, elevated ALP] and in the absence of any alternative cause[b])	– Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once 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]
	Grade 4 (AST or ALT >20×ULN and/or TB >10×ULN)	Permanently discontinue study drug/study regimen	

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis** **THIS section provides guidance only for management of "Hepatitis (elevated LFTs)" in HCC** 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**	**Any Grade** **Grade 1** (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	**General Guidance** – No dose modifications. – If ALT/AST elevations represents significant worsening based on Investigator assessment, then treat as Grade 2 event. 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**	**For Any Grade:** – 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+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient 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

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis** **THIS section provides guidance only for management of "Hepatitis (elevated LFTs)" in HCC** 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**	**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 study drug/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 study drug/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 consulting hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Sponsor's medical monitor. – 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 (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil)[a]. Discuss with Sponsor's medical monitor if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	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 study drug/study regimen dose until resolution to Grade ≤1 or baseline – Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. – Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days – Permanently discontinue study drug/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 Sponsor's medical monitor. – 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 Sponsor's medical monitor if mycophenolate motefil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-Mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis** **THIS section provides guidance only for management of "Hepatitis (elevated LFTs)" in HCC** 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**			NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	**For Grade 4:** **Same as above (except would recommend obtaining liver biopsy early)**
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 study drug/study regimen**			

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Any Grade	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, etc.) – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections etc.) – Steroids 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
	Grade 1: Serum Creatinine > 1-1.5 x baseline; > ULN-1.5 x ULN	No dose modification	For Grade 1: Monitor serum creatinine weekly and any accompanying symptom – If creatinine returns to baseline, resume its regular monitoring per study protocol. – Upon worsening treat according to severity – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 Serum Creatinine > 1.5-3.0 x baseline; > 1.5 x-3.0 x ULN	Hold study drug/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 study drug/study regimen after completion of steroid taper	For Grade 2: – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day PO or IV equivalent

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)			– 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 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] – Once serum creatinine returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol
	Grade 3 or 4 Grade 3: Serum Creatinine > 3.0 x baseline; > 3.0-6.0 x ULN Grade 4: Serum Creatinine > 6.0 x ULN)	Permanently discontinue IP/study regimen	For Grade 3-4: – 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 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 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Rash (excluding bullous skin formations)	Grade of Skin Rash	General Guidance	– Monitor for signs and symptoms of dermatitis (rash and pruritus) – **IN THE EVENT OF ANY BULLOUS FORMATION, THE SPONSOR'S MEDICAL MONITOR SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****
	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	If persistent (> 1-2 weeks) at Grade 2, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline – If toxicity worsens then treat as Grade 3 – If toxicity improves to Grade ≤ 1 or baseline then resume study drug/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, discuss with study medical monitor and promptly start systemic steroids at 1-2 mg/kg/day PO or IV equivalent – Consider skin biopsy if persistent for > 1-2 weeks or subject experiences recurrence
	Grade 3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline – If rash does not improve to ≤ Grade 1 or baseline within 30 days, then permanently discontinue Study drug/study regimen	For Grade 3 or 4: – Consult dermatologist – Promptly initiate empiric IV methylprednisolone 1-4 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, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). [a] – Consider, as necessary, discussing with Sponsor's medical monitor
	Grade 4	Permanently discontinue study drug/study regimen	

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and 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 v4.03 for defining the CTC grade/severity)	General Guidance	– Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with Sponsor's medical monitor. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behaviour changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 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 patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the Investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation): – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider 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 free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper Subjects with endocrinopathies who may require prolonged or continued steroid replacement (eg, adrenal insufficiency) can be retreated with study drug/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. Doses of prednisone are ≤10 mg/day or equivalent	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 patients 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 to 2 mg/kg/day methylprednisolone 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 study drug/study regimen interruption, and without corticosteroids. − Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. − Once patients 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] − For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (eg, adrenal insufficiency) can be retreated with study drug/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. Doses of prednisone are ≤ 10 mg/day or equivalent.	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 patients 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 IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients 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]

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Neurotoxicity (including but not limited to limbic encephalitis. autonomic neuropathy, **excluding myasthenia gravis and Guillain-Barre Syndrome)**	Any Grade (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	For Any Grade: - Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). - Monitor patient 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
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1 For sensory neuropathy/ neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1 If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study regimen can be resumed once event stabilizes to Grade ≤ 1 and after completion of steroid taper	For Grade 2: - Consider, as necessary, discussing 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 IVIG)
	Grade 3 or 4	For Grade 3: - Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. For Grade 4: - Permanently discontinue study drug/study regimen.	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 1-2 mg/kg/day or equivalent - If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg IVIG) - Once stable, gradually taper steroids over ≥ 28 days

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
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, etc.). 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 – Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 1	No dose modification	For Grade 1 – 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

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Peripheral neuromotor syndromes, such as Guillain-Barre and myasthenia gravis	Grade 2	– Hold study drug/study regimen dose until resolution to ≤ Grade 1 – Permanently discontinue study drug/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, etc.) **MYASTHENIA GRAVIS** – 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. – 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** Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 3	– Hold study drug/study regimen dose until resolution to ≤ Grade 1 – Permanently discontinue Study drug/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 – Consider, as necessary, discussing with the Sponsor's medical monitor. Recommend hospitalization – Monitor symptoms and obtain neurological consult **MYASTHENIA GRAVIS** – Steroids may be successfully used to treat myasthenia gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist.

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Peripheral neuromotor syndromes, such as Guillain-Barre and myasthenia gravis	Grade 4	Permanently discontinue study drug/study regimen	- Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. - 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:** Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
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 patients with baseline cardiopulmonary disease and reduced cardiac function. - Consider, as necessary, discussing with the Sponsor's medical monitor. - Monitor patients 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. - Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections)

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Myocarditis	Grade 1 (asymptomatic with laboratory (eg, BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/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.
	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 study drug/study regimen dose until resolution to Grade 0. – If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/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 study drug/study regimen. If Grade 3-4, permanently discontinue study drug/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 patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). [a]

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-Mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Myositis/ Polymyositis ("Poly/myositis")	Any Grade	General Guidance	For Any Grade: − Monitor patients 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 Sponsor's medical monitor. − 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 (i.e., 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 for evaluation of dysphagia or dysphonia. − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections)

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-Mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
Myositis/ Polymyositis ("Poly/myositis")	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 Sponsor's medical monitor.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	– Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/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 Sponsor's medical monitor. – 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 (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 patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Table 7: Dose Modification and Toxicity Management Guidelines for Specific Immune-Mediated Reactions (Continued)

AE	CTC Grade/Severity[a]	Dose Modifications	Toxicity Management
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	For Grade 3: Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/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 study drug/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 Sponsor's medical monitor. – 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 patient may require IVIG, plasmapheresis. Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

AChE= Acetylcholine esterase; ACTH= Adrenocorticotropin; ADL= Activities of daily living; AE= Adverse event; ALP= Alkaline phosphatase test; ALT= Alanine aminotransferase; AST= Aspartate aminotransferase; BNP= Brain natriuretic Peptide; BUN= Blood urea nitrogen; CT= Computed tomography; CTCAE= Common Terminology Criteria for Adverse Events; DILI= Drug-induced liver injury; ECG= Electrocardiography; HBcAb= Hepatitis B Antibody; HBeAg= Hepatitis B Antigen; HBsAg= Hepatitis B Australian Antigen; HBV= Hepatitis B Virus; HCC= Hepatocellular Carcinoma; HCV= Hepatitis C virus; HgA1c= Hemoglobin A1c test; IP= Investigational Product; ILD= Interstitial lung disease; imAE= immune-mediated adverse event; IG= Immunoglobulin; IV= Intravenous; GI= Gastrointestinal; LDH= Lactic acid dehydrogenase; LFT= Liver function tests; LLN= Lower limit of normal; MRI Magnetic resonance imaging; NCI= National Cancer Institute; NCCN= National Comprehensive Cancer Network; PJP= Pneumocystis jirovecii pneumonia (formerly known as Pneumocystis carinii pneumonia); PO= By mouth; T3= Triiodothyronine; T4= Thyroxine; TB= Total bilirubin; TNF= Tumor necrosis factor; TSH= Thyroid-stimulating hormone; ULN= Upper limit of normal.

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

Table 8: General Dose Modification and Toxicity Management Guidelines for Non-Immune-mediated Reactions

Non-immune-mediated Reactions		
CTC Grade/Severity[a]	**Dose Modification**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (ie. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/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 study drug/study regimen administration. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/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)	Treat accordingly as per institutional standard

AE = Adverse Events; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.
a Grade according to NCI-CTCAE version 4.03

Table 9: Dose Modification and Toxicity Management Guidelines for Non-Immune-mediated Adverse Events

AE	Toxicity Grade	Dose Modification	Toxicity Management
Any Grade	Note: dose modifications are not required for adverse events not considered to be related to IP/regimen (i.e. events due to underlying disease) or for laboratory abnormalities not considered to be clinically significant.		
Neutropenia (unless secondary to lymphomatous/CLL bone marrow involvement)	Grade 3 (ANC < 1000 cells/mm³ [1x10⁹/L])	– 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 at next scheduled dose. Otherwise, discontinue IP/study regimen	– Monitor CBC with differential at least weekly – Use of growth factors (G-CSF, GM-CSF) is permitted as per ASCO or – ESMO Guidelines
	Grade 4 (ANC < 500 cells/mm³ [0.5x10⁹/L])	– Decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the Sponsor	– Monitor CBC with differential at least weekly – Use of growth factors (G-CSF, GM-CSF) is permitted as per ASCO or ESMO Guidelines
Thrombocytopenia (unless secondary to lymphomatous/CLL bone marrow involvement)	Grade 3 (Platelets < 50,000 cells /mm³ [50×10⁹/L])	– 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 at next scheduled dose. Otherwise, discontinue IP/study regimen	– Monitor CBC with differential at least weekly – Platelet transfusion is permitted as per ASCO Guidelines
	Grade 4 (Platelets < 25,000 cells /mm³ [25x10⁹/L])	– Decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the Sponsor	– Monitor CBC with differential at least weekly – Platelet transfusion is permitted as per ASCO Guidelines
Stevens-Johnson Syndrome or toxic epidermal necrosis		– Discontinue all the agents	

Table 9: Dose Modification and Toxicity Management Guidelines for Non-Immune-mediated Adverse Events (Continued)

AE	Toxicity Grade	Dose Modification	Toxicity Management
Venous thrombosis/ embolism	Grade 3 or 4	– If 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 durvalumab administration at next scheduled dose. Otherwise, discontinue durvalumab – If Grade 4, discontinue durvalumab	– Start anticoagulation treatment
Early anti-tumor response (eg pseudotumor progression or flare reaction)	Grade 1 or 2	– Continue IP/regimen	– At the Investigator's discretion may initiate therapy with NSAIDs, limited duration corticosteroids, and/or narcotics
	Grade 3 or 4	– Hold IP/regimen – If symptoms resolve to ≤ Grade 1, resume the IP/regimen	– Initiate therapy with NSAIDs, corticosteroids, and/or narcotics
	Grade 3 or 4	– Hold IP/regimen – If symptoms resolve to ≤ Grade 1, resume the IP/regimen	– Initiate therapy with NSAIDs, corticosteroids, and/or narcotics
Other AEs (continued)	Grade 3 or 4	For 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 at next scheduled dose. Otherwise, discontinue IP/study regimen For 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)	– Treat accordingly as per local/institutional guidelines

AE = adverse event; ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; CBC = complete blood count; CLL = chronic lymphocytic leukemia; ESMO = European Society of Medical Oncology; G CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IP = investigational product; L = liter; mm = millimeter; NSAID = non-steroidal anti-inflammatory drug;

Table 10: Dose Modification and Toxicity Management Guidelines for Infusion- related Reactions

Toxicity	Severity	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)
	Grade 1	– The infusion rate of study drug/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 – Pre-medicate prior to rituximab doses – Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions
	Grade 2	– The infusion rate of study drug/regimen may be decreased 50% or temporarily interrupted until resolution of the event (up to 4 hours) – Subsequent infusions may be given at 50% of the initial infusion rate	
	Grade 3 or 4	– Permanently discontinue durvalumab or study drug 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)

IM = intramuscular; IP = investigational product; IV = intravenous.

7.2.5.3. Dose Modifications Guidelines for R-CHOP

Dose reductions of the R-CHOP regimen or any of the drugs included in the treatment regimen are not allowed except for vincristine as described in Table 12.

Should there be a treatment-related AE requiring interruption of R-CHOP administration on Day 1 of any scheduled treatment cycle (R-CHOP is scheduled for 6 to 8 cycles), the infusion will be held until resolution of the AE. If the events resolve adequately by Day 7 of a cycle, R-CHOP can be administered up to Day 8 of the cycle. However, if the AEs do not resolve by

Day 8 of the cycle, R-CHOP will be held until Day 1 of the next cycle. Any missed doses of R-CHOP will not be made up at a later time.

Table 11: Dose Modification Rules for Vincristine

NCI-CTCAE Toxicity Grade	Action Required
Peripheral neuropathy Newly developed ≥ Grade 3 (applies only to those neuropathies which begin or worsen while on study)	• Hold (interrupt dose) • When the toxicity resolves to ≤ Grade 2 or to baseline, restart at the next lower dose level

NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 12: Dose Reduction Levels for Vincristine

Starting Dose	1.4 mg/m^2 (maximum of 2.0 mg total)
Level –1 Dose	1.0 mg max

7.2.5.4. Dose Modifications Guidelines for Lenalidomide

No newly enrolled subjects are to be treated with the combination of durvalumab, R-CHOP plus lenalidomide. Only those subjects currently enrolled and receiving clinical benefit, based on the discretion of the Investigator, are eligible to remain on treatment following reconsent.

Dose modifications (interruption and dose reduction) of lenalidomide are allowed for AEs associated with known lenalidomide-related toxicities. Treatment-related AEs and the severity which require protocol-defined dose modifications of lenalidomide are found in Table 14.

The dose of lenalidomide may be reduced successively by one level from the starting dose according to Table 13. No more than one dose level reduction per cycle is permitted unless discussed with and approved after consultation with the Celgene Medical Monitor. No dose re-escalation of lenalidomide is permitted at any time during the study treatment. In addition, if a subject continues to experience unacceptable toxicity at the lowest dose level allowed, lenalidomide will be discontinued permanently.

Table 13: Lenalidomide Dose Modification Levels

Dose[a]	Induction Treatment Once Daily on Days 1-14 of 21-day Cycle
Level 1	15 mg
Level −1	10 mg
Level −2	5 mg
Level −3	2.5 mg
Level −4	Discontinue

[a] Once a subject's dose has been reduced, no dose re-escalation will be permitted

Table 14: Dose Modification Schedule for Lenalidomide-related Adverse Events

Dose Modifications (Interruption/Reduction) NCI-CTCAE (v 4.03) Toxicity Grade	Action Required
Neutropenia[a] Sustained (≥ 7 days) Grade 3 OR ≥ Grade 3 associated with fever (temperature ≥ 38.5°C) OR Grade 4	• Withhold dose • Monitor CBC at least every seven days • If neutropenia has resolved to ≤ Grade 2 on first occurrence, restart at the same dose level • If neutropenia has resolved to ≤ Grade 2 on subsequent occurrences, restart at the next lower dose level
Thrombocytopenia [a] ≥ Grade 3 (platelet count < 50,000 cells/mm³ [50x10^9/L])	• Withhold dose • Monitor CBC at least every seven days • If thrombocytopenia resolves to ≤ Grade 2 on first occurrence, restart at the same dose level • If thrombocytopenia resolves to ≤ Grade 2 on subsequent occurrences, restart at next lower dose level
Rash Grade 2 or 3 non-desquamating (blistering) --- Desquamating (blistering) ≥ Grade 3 OR Non-desquamating Grade 4	• Determine causative investigational product and if attributable to lenalidomide then: • Hold dose; administer antihistamines or short course of ≤ 20 mg prednisone (or equivalent) • When toxicity resolves to ≤ Grade 1, restart at the same dose level --- • Determine causative investigational product and if attributable to lenalidomide then: • Discontinue lenalidomide
Allergic reaction or hypersensitivity Grade 2	• Determine causative investigational product and if attributable to lenalidomide then: • Withhold dose. Follow at least every seven days
--- Grade 3-4	• When the toxicity resolves to ≤ Grade 1, restart lenalidomide at next lower dose level --- • Discontinue lenalidomide
Constipation Grade 1-2 --- ≥ Grade 3	• Initiate bowel regimen and maintain dose level --- • Withhold dose. Follow at least every seven days • When the toxicity resolves to ≤ Grade 2, restart at same dose level

Table 14: Dose Modification Schedule for Lenalidomide-related Adverse Events (Continued)

Dose Modifications (Interruption/Reduction) NCI-CTCAE (v 4.03) Toxicity Grade	**Action Required**
Venous thrombosis/embolism ≥ Grade 3	• Withhold dose and start therapeutic anticoagulation; restart at the same dose level at Investigator's discretion
Tumor Lysis Syndrome *Grading is per Cairo-Bishop, and not per NCI-CTCAE,* for TLS only Lab TLS or Grade 1 TLS ---------- Grade 2-4	• Continue lenalidomide at the same dose level, OR at the Investigator's discretion, continue lenalidomide and reduce dose by one level • Provide vigorous IV hydration and appropriate medical management according to the local standard of care, until electrolyte abnormalities are corrected. Rasburicase therapy is appropriate (if approved by the local Health Authority) as needed to reduce hyperuricemia • Hospitalization will be at Investigator's discretion ---------- • Withhold dose • When symptoms resolve to Grade 0, restart at same dose level • If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following re-initiation of lenalidomide
AST or ALT > 3 x ULN	• Withhold lenalidomide dose; re-test at least weekly until AST or ALT < 2.5 x ULN or return to baseline • If the event is considered related to lenalidomide, restart lenalidomide at next lower dose level • If the event is considered NOT related to lenalidomide, restart at the same dose level of lenalidomide • For subjects with Gilbert's syndrome or liver involvement, consult the Celgene Medical Monitor regarding dose reductions
Bilirubin > 3 x ULN	• Withhold lenalidomide dose; re-test at least weekly until bilirubin < 1.5 x ULN • If the event is considered related to lenalidomide, restart lenalidomide at next lower dose level • If the event is considered NOT related to lenalidomide, restart at the same dose of lenalidomide • For subjects with Gilbert's syndrome or liver involvement, consult the Celgene Medical Monitor regarding dose reductions
Other lenalidomide related non-hematologic AEs ≥ Grade 3	• Withhold dose • When the AE resolves to ≤ Grade 2, restart at the same or next lower dose level per the Investigator's discretion

AE = adverse event, ALT = alanine transaminase; AST = aspartate transaminase; CBC = complete blood count, NCI-CTCAE = National Cancer Institute Common Terminology Criteria for AE, Lab = laboratory, TLS = tumor lysis syndrome; ULN = upper limit of normal

[a] Unless secondary to lymphoma bone marrow involvement per Investigator assessment.

7.2.6. Overdose

Overdose, as defined for this protocol, refers to durvalumab, lenalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone. 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

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.

7.3. Method of Treatment Assignment

Interactive response technology will be employed to manage subject medications.

7.4. 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.

7.5. 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.

7.6. Investigational Product Compliance

For the oral medications of lenalidomide and prednisone/prednisolone, 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 container, 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 reconciliation of capsules/tablets will be done upon return of the investigational product container. Subject compliance will be noted in the source records and on the appropriate CRFs based upon the interview and capsule/tablet count.

For the IV medications of durvalumab, rituximab, cyclophosphamide, doxorubicin and vincristine, the planned 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 study treatments or disease progression. Supportive care, including but not limited to anti-emetic 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 IP until 90 days after the last dose of durvalumab or 28 days after the last dose of any other IP, whichever is later, must be reported on the CRF.

For subjects who are treated with lenalidomide in this study (Arm B: durvalumab in combination with lenalidomide and R-CHOP), please refer to the lenalidomide prescribing information, the Summary of Product Characteristics or the IB for potential drug interactions. In particular, caution should be exercised with the concomitant use of digoxin and statins. Although the coadministration of lenalidomide with the P-glycoprotein inhibitors quinidine or temsirolimus had no clinically relevant effect on the pharmacokinetics of lenalidomide, the concomitant use of P-glycoprotein inhibitors (eg verapamil, cyclosporin A, reserpine, quinidine, yohimbine, tamoxifen, toremifena) should be considered carefully.

For information regarding other drugs that may interact with IP and affect its metabolism, pharmacokinetics, or excretion, please see the IBs and/or local package inserts.

8.1. Permitted/Recommended Concomitant Medications and Procedures

Investigators may prescribe concomitant medications or treatments necessary to provide adequate supportive care except for those medications identified as “prohibited” as listed in Section 8.2.

Specifically, subjects should receive full supportive care during the study, including but not limited to, transfusions of blood and blood products, treatment with antibiotics, antiemetics, antidiarrheals, analgesics, and other treatments considered necessary based on the clinical judgment of the treating physician, and in accordance with institutional standards.

8.1.1. Infection Prophylaxis

Investigators may use their discretion in administering infection prophylaxis for subjects regarded to be at high risk (including but not limited to: acyclovir or similar drug for herpes zoster). Monitoring of subjects for fever, neutropenia and infections and treatment with appropriate anti-infective therapy should be instituted as clinically indicated.

8.1.2. Venous Thromboembolism Prophylaxis (Lenalidomide)

It is not known whether prophylactic anticoagulation 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.

8.1.3. Nausea Prophylaxis

Premedication with an antiemetic is recommended according to local practice.

8.1.4. Infusion Reaction Prophylaxis (Rituximab and 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.

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 durvalumab.

General guidelines for dose modification due to infusion reactions are found in Table 10.

8.1.5. Treatment of Early Anti-Tumor Response (Tumor Flare Reaction)

Early anti-tumor response (eg pseudotumor progression, tumor flare reaction) is defined as a sudden increase in the size of the disease bearing sites, including the lymph nodes, spleen and/or the liver often accompanied by a low-grade fever, tenderness and swelling, diffuse rash and in some cases, an increase in the peripheral blood lymphocyte counts. Treatment is based on the clinical judgment of the Investigator. TFR will be graded using NCI-CTCAE Version 3.0. Symptomatic treatment of Grade 1 and 2 events with non-steroidal anti-inflammatory drugs (NSAIDs) (ie, ibuprofen), corticosteroids, and/or narcotic analgesics for pain management is recommended, without an interruption in study drug administration.

In the event of a ≥ Grade 3 early anti-tumor response, it is recommended that IP should be interrupted, as indicated, and the event treated with corticosteroids, NSAIDs, narcotic analgesics, and or antihistamines. Refer to Table 9 for further instructions and dose modifications for Grade 3 and 4 events.

8.1.6. Urotoxicity Prophylaxis (Cyclophosphamide)

Urotoxicity including hemorrhagic cystitis, pyelitis, ureteritis, and haematuria have been reported with cyclophosphamide therapy. Prior, during and immediately after the administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity. Adequate treatment with mesna and/or strong hydration to force diuresis can markedly reduce the frequency and severity of bladder toxicity. Please refer to the cyclophosphamide prescribing information for further details.

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 prohibited concomitant medications during the study. The Sponsor must be notified if a subject receives any of these during the study:

- Any investigational anti-cancer therapy.
- Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment.
- Concurrent Radiotherapy with the exception of post-induction radiotherapy if prespecified during the screening period (Section 7.2.2). Response-adapted radiotherapy is not permitted.
- Concurrent use of hormones or high dose corticosteroids as anti-cancer therapy is prohibited. However, these treatments may be permitted for treating AEs, certain chronic conditions, and/or other non-cancer-related conditions as clinically necessary (eg insulin for diabetes and hormone replacement therapy).
- Based on the observation in subjects with multiple myeloma who had an increased risk of venous thromboembolism when treated with lenalidomide in combination with dexamethasone, combined oral contraceptive pills are not recommended in this clinical study. If a subject is already using combined oral contraception at study entry, she should switch to one of the highly effective methods listed in Section 4.2 , however, the risk of venous thromboembolism continues to be increased for 4 to 6 weeks after discontinuing combined oral contraception.
- Copper-releasing 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.
- 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) inhibitors.

  Note: 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
- Live attenuated vaccines during the study and for 12 months after last dose of rituximab or until recovery of B-cells and for 120 days after last dose of durvalumab, whichever is longer.
- Herbal and natural remedies are to be avoided.
- Prophylactic treatment for CNS disease with IV drugs is not permitted during the course of the study treatment period.

8.3. Required Concomitant Medications and Procedures

8.3.1. Mandatory Supportive Therapy

Appropriate pre-infusion medications according to the package insert or institutional standards is required prior to administration of intravenous study treatments.

8.3.2. CNS Prophylaxis

Subjects at high risk for CNS involvement, as defined in the NCCN guidelines and CNS evaluation in Section 6.1 must receive CNS lymphoma prophylaxis treatment with intrathecal drugs (eg methotrexate, cytarabine) as per NCCN guidelines or per institutional standards. Prophylactic treatment for CNS disease with IV drugs is not permitted during the course of the study treatment period.

8.3.3. TLS Prophylaxis

Treatment with allopurinol (or equivalent as per institutional guidelines) and hydration for TLS prophylaxis is required during the first week of study treatment and should initiate at least 3 days prior to the first study drug treatment (C1D1). 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 monitored by blood chemistry laboratory analysis and assessed by the Cairo-Bishop Grading system (Appendix D). The assessment includes both laboratory tumor lysis syndrome (LTLS) and clinical TLS criteria. Subjects experiencing LTLS or clinical TLS should receive appropriate medical management according to the institutional standard of care.

8.3.4. Pneumocystis Jirovecii Prophylaxis

Pneumocystis jirovecii prophylaxis is required (including but not limited to trimethoprim/sulfamethoxazole) and should follow local practice.

8.3.5. Neutropenia Prophylaxis

All subjects allocated to Arm B should receive neutropenia prophylaxis with G-CSF.

For subjects allocated to Treatment Arm A, primary neutropenia prophylaxis with G-CSF should follow local practice.

Both G-CSF and pegylated G-CSF are allowed. Other growth factors (eg erythropoietin) may be prescribed at any time during the Treatment and Follow-up Periods at the Investigator's discretion once a subject has experienced cytopenic or myelosuppressive events.

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 transfusions of blood or blood products cannot be administered during the Screening period to increase a subject's blood values in order to meet entry criteria.

8.3.6. Hepatitis B Virus Reactivation Prophylaxis

In subjects with prior HBV infection, HBV reactivation may occur during or after rituximab 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 or lenalidomide treatment. Such subjects should be monitored for clinical and laboratory signs of hepatitis (eg elevation in liver enzymes) and/or HBV reactivation during and following rituximab 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 2, two-arm, open-label study is designed to evaluate the clinical activity, safety, and tolerability of durvalumab in combination with R-CHOP or in combination with R2-CHOP followed by durvalumab consolidation therapy in previously untreated subjects with high-risk DLBCL within each COO subtype (non-ABC and ABC). It is also intended to identify biomarkers that predict response to the study treatment.

The study is divided into a *Safety Run-in Stage* to evaluate the safety of the treatment combinations until at least 10 subjects have completed at least one cycle of study treatment or discontinued prematurely followed by an *Expansion Stage* (to complete study enrollment) to analyze the clinical activity of the treatment combinations in up to approximately 40 total subjects in the efficacy evaluable population.

Following Partial Clinical Hold instituted by the US FDA which affects Arm B, the *Safety Run-in Stage* will evaluate safety of the treatment Arm A combinations when at least 10 subjects have been included into Arm A and have been treated for at least one cycle of study treatment or discontinued prematurely.

The primary objective of this study is to assess the clinical activity of durvalumab in combination with R-CHOP or in combination with R2-CHOP in previously untreated subjects diagnosed with high-risk DLBCL.

The secondary objectives are:

- To examine the safety and tolerability of durvalumab when given in combination with R-CHOP or R2-CHOP followed by durvalumab consolidation in the treatment of previously untreated subjects with high-risk DLBCL
- To identify and develop biomarkers of the tumor microenvironment and of the host immune system which are predictive of clinical response to durvalumab, when administered in combination with R-CHOP or R2-CHOP, followed by durvalumab consolidation therapy that will be tested in further randomized clinical trials. Examples of defined analytical methods that may be investigated include, but are not limited to:
  - PD-L1 IHC
  - Gene Expression Signatures

The primary efficacy analysis will evaluate the complete response rate (CRR) at the end of the induction therapy in the efficacy evaluable population in a comparative manner against historical control.

The key secondary efficacy analysis will evaluate the rate of subjects who continue consolidation therapy out of all subjects in the efficacy evaluable population in a comparative manner against historical control.

If null hypothesis on primary endpoint is rejected, hypothesis testing on the key secondary endpoint will be performed hierarchically without any type I error adjustment.

Analysis of other secondary efficacy endpoints will include further analysis of response and progression data and correlative evaluation of biomarkers (as described in Section 6.8) as predictive with clinical responsiveness.

The statistical analysis of the safety profile will be observational in nature.

On 05 Sep 2017, a Partial Clinical Hold was placed to this study by US FDA. The decision by the FDA was based on risks identified in other trials for pembrolizumab, an anti-programmed cell death-1 (PD-1) antibody, in patients with multiple myeloma in combination with immunomodulatory agents. As a result of the US FDA Partial Clinical Hold, enrollment continued into Arm A only and new subjects received induction therapy (durvalumab + R-CHOP) after Cycle 1 regardless of DLBCL COO subtype. Enrollment into Arm B (durvalumab in combination with [R2-CHOP]) was discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who were receiving clinical benefit, based on the discretion of the investigator, could continue study treatment after being reconsented.

9.2. Study Population Definitions

The statistical analysis populations are defined as follows.

- Safety Population: All subjects who take at least one dose of IP. Reporting done on Safety Population will be done against actual treatment received.
- Efficacy Evaluable Population: All subjects who complete at least one cycle of their assigned treatment, have a baseline assessment by CT scan and have 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 post-dose biomarker assessment. Reporting done on Biomarker Evaluable Population will be done against actual treatment received.

9.3. Sample Size and Power Considerations

The total sample size for the study is estimated to be approximately 45 subjects enrolled (with approximately 40 subjects in the efficacy evaluable population).

Assuming historical control data of 55% for the complete response rate at the end of the induction therapy in the efficacy evaluable population when treated with R-CHOP and 75% for the complete response rate at the end of the induction when durvalumab is added to R-CHOP, 40 subjects would provide ~71% power to reject the null hypothesis that the complete response rate at the end of the induction therapy in the efficacy evaluable population is less than 55%. If null hypothesis on the primary endpoint is rejected, hypothesis testing on the rate of subjects who continue consolidation therapy in the efficacy evaluable population will be performed hierarchically without any type I error adjustment. Assuming that the rate of subjects who continue consolidation when durvalumab is added to R-CHOP is at 85%, 40 subjects would provide in this hierarchical testing strategy ~43% power to reject the null hypothesis that the rate

of subjects who continue consolidation therapy in the efficacy evaluable population is less than 70%.

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

The clinical activity of the study treatments will be evaluated from a baseline assessment collected during Screening prior to the start of treatment, until a subject meets the criteria for disease progression.

All efficacy evaluable subjects will be included for efficacy analysis.

Efficacy analysis will be performed for each treatment arm by combining data from both the *Safety Run-in Stage* and the *Expansion Stage* of the study. Subgroup analysis for efficacy evaluation will be summarized. This includes sex, age category and prognostic risk criteria for each treatment arm.

The primary endpoint of this study is the complete response rate at the end of the induction therapy. The key secondary endpoint is the rate of subjects who continue consolidation therapy out of all subjects.

The CRR and the rate of subjects who continue consolidation therapy will be summarized using count and percentage. The 95% confidence 2-sided confidence interval will be based on the Clopper-Pearson approach. Null hypothesis for the primary endpoint will be rejected if the lower limit of the confidence interval for the complete response rate at the end of the induction therapy in the efficacy evaluable population is above 55%. If null hypothesis for the primary endpoint is rejected, then hypothesis testing can be performed on the key secondary endpoint without any type I error adjustment. Null hypothesis for the key secondary endpoint will be rejected if the lower limit of the confidence interval for the rate of subjects who continue consolidation therapy out of all subjects in the efficacy evaluable population is above 70%.

The secondary efficacy endpoint will consist of an analysis of clinical responses to study treatment in biomarker-defined subpopulations. Clinical responses will be assessed for potential relationship to biomarker positive subjects and biomarker negative subjects. Other efficacy analyses included in the exploratory analysis will include PFS rate at 12 months, PFS rate at 24 months, CR rate at end of treatment (12 months). Progression-free survival is calculated as the time from C1D1 to the first documented progression or death due to any cause during the entire

efficacy evaluation period. The PFS from first dose of any IP to 12 or 24 months after the first dose of any IP will be summarized from Kaplan-Meier method and its 95% confidence interval will also be provided.

9.7. Safety Analysis

Safety analysis will include all subjects in the Safety population. Investigational product exposure will be summarized for each treatment arm including duration of IP, 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 for all subjects combined.

9.7.1. Adverse events

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and graded according to NCI-CTCAE version 4.03 with the exception of the evaluation of TFR which will be graded according to NCI-CTCAE version 3.0. 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 term and AE of special interest (Section 10.7) for a subject will be utilized for summaries of AEs by NCI-CTCAE grade.

Subsets of AEs to be summarized include AEs of special interest (AESI), SAEs, suspected treatment-related AEs, AEs that resulted in withdrawal of investigational product and AEs that resulted in death.

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.

9.7.2. Laboratory Evaluations

Summaries of laboratory data will be based on observed data and will be reported using conventional units. Baseline, raw values, and changes from baseline will be summarized using descriptive statistics for each laboratory test specified in the study protocol at each post-baseline visit by treatment arm.

Laboratory data will be graded according to NCI-CTCAE severity grade. For variables for which an NCI-CTCAE grade 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 arm.

The frequencies of the worst severity grade observed during treatment will be displayed in cross-tabulations by baseline status for each treatment arm. Shift tables will be presented showing the change in severity grade from baseline to each post-baseline visit and to the maximum post-baseline grade during the induction phase and consolidation phase.

9.8. Interim Analysis

No formal interim analysis planned in this study.

Primary analysis was run as planned based on the 02 Aug 2018 data cutoff, therefore, following the decision to discontinue the Follow-up Period and stop the follow-up data collection in the clinical database, no additional efficacy or safety statistical analyses will be performed after the primary analysis.

9.9. Other Topics

The PK and Pd/ biomarker analysis will be specified in separate analysis plan.

9.9.1. Safety Review Committee

A SRC will be convened to evaluate the safety profile and tolerability of the *Safety Run-in Stage* as well as potentially other safety data in this clinical study, see Section 6.5.2.

9.9.2. Steering Committee

The conduct of this study will be overseen by a global scientific steering committee (GSSC), presided over by the coordinating Principal Investigator(s) and if possible the lead Investigators from each country 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.

9.9.3. Exploratory Analysis

Planned exploratory analyses include:

- PFS at 12 months;
- PFS at 24 months;
- CR rate at 12 months;
- The PK/Pd relationship for durvalumab when given in combination with R-CHOP or with R2-CHOP followed by durvalumab consolidation;
- Pharmacodynamic and mechanistic biomarkers for durvalumab and lenalidomide when given in combination with R-CHOP or with R2-CHOP followed by durvalumab consolidation therapy will be explored

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 pre-existing 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 7.2.6 for the definition of an 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, rituximab, cyclophosphamide, vincristine, doxorubicin or prednisone 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 after the last dose of durvalumab or 28 days after the last dose of any other IP, whichever is later, as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. 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 last durvalumab subject's 90-day Safety Follow-up Visit (data cutoff date 06 Jun 2019), AEs and SAEs are no longer required to be collected in the CRFs.

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
- 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 pre-existing 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 IP, action taken regarding the IP, 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 minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. However, TFR will be graded using NCI-CTCAE version 3.0.

AEs that are not defined in the 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 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 caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP 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, for example, 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 β-subunit of human chorionic gonadotropin (β-hCG) 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, 12 months after the last dose of rituximab, or 28 days after last dose of lenalidomide, are considered immediately reportable events.

Investigational product is to be discontinued immediately (please also see Section 11.1) and the subject instructed to return any unused portion of lenalidomide or prednisone/prednisolone 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 after the last dose of durvalumab or 28 days after the last dose of any other IP, whichever is later) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. 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.

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 five (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 IB.

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 components of the study treatment (ie, rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone/prednisolone,) based on the EU Summary of Product Characteristics (SmPC). Any SAE that is suspected of being related to local Involved-Field Radiation Therapy (IFRT) alone will not be assessed for expectedness or reported in an expedited manner.

Events of disease progression for the disease under study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as expected adverse events and will not be reported as expedited safety reports to regulatory authorities.

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 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 understanding of the Investigational Product and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy.

An 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 regard to an adverse event (AE) being an imAE, the Investigator should promptly contact the Medical Monitor.

10.7.1. AESIs for Durvalumab

The AESIs reported for durvalumab are AEs that include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism that may require more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy. Early recognition of signs and symptoms potentially related to an inflammatory or immune-mediated mechanism is important for proper management of toxicities.

The AESIs observed with anti PD-L1/PD-1 agents such as durvalumab include diarrhea/colitis, pneumonitis/ILD, hepatitis and increases in transaminases, endocrinopathies, dermatitis/rash and pruritus, nephritis and increases in serum creatinine, neuromuscular toxicity such as myasthenia gravis and Guillain-Barre, and pancreatitis. These are described below in more detail.

For guidance on identifying, evaluating, and treating AESIs see the toxicity management guidelines (Table 6, Table 7, Table 8, Table 9, Table 10).

Further information on these AESIs (eg, presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure.

10.7.2. AESIs for Lenalidomide

The AESIs defined for lenalidomide in this study are Second Primary Malignancies (SPM), Deep Vein Thrombosis (DVT), and Tumor Flare Reaction (TFR). These AESIs are described below in more detail.

Further information on the AESIs for lenalidomide can be found in the current version of the lenalidomide IB and in the lenalidomide prescribing information.

10.7.2.1. Second Primary Malignancies

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 study treatment; 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 last durvalumab subject's 90-day Safety Follow-up Visit (data cutoff date 06 Jun 2019), SPMs will no longer be collected in the CRFs. Subjects who received lenalidomide will continue to be followed for SPMs as required by this study protocol (Section 3.1.3.1) [redacted]. Investigators will continue to record SPMs in the subject's source documents and report SPM events to Celgene Drug Safety. After stopping data collection in the clinical database, any SPM events will continue to be collected in the safety database.

10.7.2.2. Deep Vein Thrombosis

Factors known to increase thrombotic risk in cancer patients in general, not necessarily those receiving lenalidomide, include but are not limited to the underlying disease, family history, age, obesity, immobilization, hormonal therapy, central venous catheter, recent DVT, and doxorubicin (Zhou, 2010; Park, 2012; Lyman 2013).

Although available data with lenalidomide monotherapy in lymphoma patients show a lower incidence of VTE compared with lenalidomide in combination with dexamethasone in multiple myeloma subjects, it is recommended that all subjects at risk for thromboembolic events receive anti-thrombotic prophylaxis (see Section 8.1.2), and all subjects will be closely monitored for VTE.

10.7.2.3. Tumor Flare Reaction / Pseudoprogression

Tumor flare reaction is an adverse effect of lenalidomide typically occurring in the first cycle (Chanan-Khan, 2008a; Witzig, 2009). It is important to note that the increased lymphadenopathy seen in TFR may mimic PD. Therefore, careful monitoring and evaluation to differentiate TFR from PD is necessary for addressing treatment of individual subjects including making decisions to discontinue treatment (Chanan-Khan, 2008b). There are currently no laboratory or radiological tests that distinguish TFR from PD. The distinction may be made on clinical grounds, incorporating observations such as timing of the event relative to the start of lenalidomide, associated physical findings, laboratory findings, and pace of disease before and after institution of lenalidomide treatment. Also, in case of TFR, inflammation and edema may reduce or disappear after short term treatment with NSAIDs and/or corticosteroids.

Management of TFR is described in Section 8.1.5.

10.7.3. Other AESIs

Other AESIs defined in this study are Infusion-Related Reactions and Allergic Reactions, Tumor Lysis Syndrome (TLS), and Myelosuppression. These AESIs can be related to any of the study treatments including backbone therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

These AESIs are described below in more detail.

10.7.3.1. Infusion-Related Reaction, Anaphylaxis and Allergic Reactions

With the administration of monoclonal antibodies, major safety concerns associated with immunogenicity include serious allergic reactions and anaphylaxis, cytokine-release syndrome, infusion-related reactions, and delayed hypersensitivity associated to immune complex disease, which can potentially be severe or life-threatening leading to death.

Adverse reactions that occur during or shortly after infusion may include fever, chills, hypotension, dyspnea, tachycardia, cyanosis, respiratory failure, urticaria and pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension rash, headache, flushing, sweating, myalgia, nausea, vomiting, unresponsiveness, and hemodynamic instability. The typical onset can be within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to the agent, but between 10% and 30% occur during subsequent treatments (Lenz, 2007).

Anaphylaxis is a systemic, immediate hypersensitivity reaction that is mediated by interactions between factors released from IgE and mast cells; these interactions result in an antigen/antibody reaction. Clinical manifestations of acute allergic reactions may range from localized skin reactions at the injection site to AEs, which can include, but are not limited to, those events

similar to infusion-related reactions to severe reactions including anaphylaxis and drug hypersensitivity syndromes. These reactions may be more common with higher rates of infusion, and in patients with a history of allergies.

Patients should be closely monitored during and after infusions. Severe hypersensitivity reactions should be managed according to standard clinical practice, and medical equipment and staff trained to treat acute anaphylactic reactions must be immediately available at all sites that perform mAb infusions.

10.7.3.2. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a well-known constellation of metabolic abnormalities resulting from spontaneous or treatment-related tumor necrosis or fulminant apoptosis. The metabolic abnormalities include: hyperkalemia, hyperuricemia and hyperphosphatemia with secondary hypocalcaemia with risk of renal failure. TLS has been reported in subjects receiving rituximab plus lenalidomide and rituximab plus chemotherapy.

The presence of known risk factors such as bulky disease, pre-existing (moderate) renal insufficiency, high ALC and high uric acid levels (> 8 mg/ dL) prior to therapy are known to increase the likelihood of TLS. Early identification of subjects at risk and the prevention of TLS development with the initiation of preventive measures, as well as the careful monitoring for early signs of laboratory TLS and the prompt initiation of supportive care are critical to prevent potentially life-threatening metabolic derangements (Cairo, 2010).

Management of TLS is described in Section 8.3.3.

10.7.3.3. Myelosuppression

Myelosuppression is the major toxicity of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen in the treatment of diffuse large B-cell lymphoma and can present as decrease in the WBC count, decrease in the platelet count, decrease in the hemoglobin concentration, or any combination of those.

Particularly neutropenia and febrile neutropenia (FN) are serious hematologic toxicities of chemotherapy containing myelotoxic agents, and prolonged FN may increase disease-related morbidity and mortality.

Management of myelosuppression is described in Table 9. Please also refer to Section 8.3.5 for the use of neutropenia prophylaxis with G-CSF.

10.8. 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

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Treatment was completed per protocol
- Adverse event(s)
- Pregnancy (please also see Section 10.4.1)
- Disease progression
- Protocol violation
- Withdrawal of consent
- Lost to follow up
- Death
- 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 Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Disease progression
- Adverse event
- Protocol violation
- Withdrawal of consent
- Screen failure
- Lost to follow up
- Death
- 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 Physician(s) 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 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-investigators 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 reconsented 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 last durvalumab subject's 90-day Safety Follow-up Visit date (data cutoff date 06 Jun 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 standard operative procedures (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 last durvalumab subject's 90-day Safety Follow-up Visit date (data cutoff date 06 Jun 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 Food and Drug Administration [FDA] and European Medicines Agency [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.

15.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the patient. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect,

seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing [redacted] or by contacting the Celgene Customer Care Center [redacted].

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, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

17. REFERENCES

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18. APPENDICES

Appendix A: Table of Abbreviations

Table 15: Table of Abbreviations

Abbreviation or Specialist Term	Explanation
ABC	Activated B-cell
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activity of daily life
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
anti-HBc	Antibody to the hepatitis B core antigen
Anti-HBs	HBV surface antibody
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase (SGOT)
β-hCG	β-subunit of human chorionic gonadotropin
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BSA	Body surface area
BUN	Blood urea nitrogen
C	Cycle
CBC	Complete blood count
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
COO	Cell of origin
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form

Table 15: Table of Abbreviations (Continued)

Abbreviation or Specialist Term	Explanation
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	Cytotoxic T-lymphocyte-associated antigen
D	Day
DEL	Double-expressor lymphoma
DHL	Double-hit lymphoma
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EFS	Event-free survival
EOI	End of infusion
EOT	End of treatment
ESMO	European Society for Medical Oncology
FCBP	Female subjects of childbearing potential
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
FL	Follicular lymphoma
GCB	Germinal center B-cell
G-CSF	Granulocyte-Colony stimulating factor
GEP	Gene expression profiling
GCP	Good Clinical Practice
GM-CSF	Granulocyte Macrophage-Colony stimulating factor

Table 15: Table of Abbreviations (Continued)

Abbreviation or Specialist Term	Explanation
GSSC	Global scientific steering committee
HBsAg	HBV surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
imAE	Immune-mediated adverse event
IMiD	Immunomodulatory drug
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product
IPI	International Prognostic Index
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
IWG	International Working Group
LDH	Lactic acid dehydrogenase
LST	Lymphoma subtyping test
LTLS	Laboratory tumor lysis syndrome
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MRI	Magnetic resonance imaging
MUGA	Multi gated acquisition scan

Table 15: Table of Abbreviations (Continued)

Abbreviation or Specialist Term	Explanation
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NOS	Not otherwise specified
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
Pd	Pharmacodynamic(s)
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Oral administration
PR	Partial response
PTT	Partial thromboplastin time
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
R-CHOP	Rituximab plus CHOP
R2-CHOP	Lenalidomide plus R-CHOP
SAE	Serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SPM	Second primary malignancies
SRC	Safety Review Committee

Table 15: Table of Abbreviations (Continued)

Abbreviation or Specialist Term	Explanation
SUSAR	Suspected unexpected serious adverse reaction
THL	Triple-hit lymphoma
TIL	Tumor-infiltrating lymphocytes
TLS	Tumor lysis syndrome
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
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 16: 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

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 17: 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
Non-measured 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
Non-measured 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 17: 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
Non-measured 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 Extranodal lesions	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic 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
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions

Table 17: 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

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 de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (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. Non-measured 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: Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Performance Status (Oken, 1982) will be scored according to Table 18.

Table 18: Performance Status by Eastern Cooperative Oncology Group Scale

Score	Description
0	Fully active, able to carry on all pre-disease 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.

Appendix D: Cairo-Bishop Definitions of Tumor Lysis Syndrome

Table 19: 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 subject has or will receive adequate hydration (± alkalinization) and a hypouricemic agent(s).

Table 20: 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 21: Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrhythmia	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]

ADL= activities of daily living; LTLS = laboratory tumor lysis syndrome; TLS= tumor lysis syndrome; ULN = upper limit of normal.
[a] Probably or definitely attributable to clinical TLS.
Source: Cairo, 2004

Appendix E: Lenalidomide Pregnancy Prevention Risk Management Plan

The Pregnancy Prevention Risk Management Plan is a standalone document.

Appendix F: Prognostic Indexes for Patients With DLBCL (IPI and NCCN-IPI) and to Assess Risk of CNS Disease

Table 22: International Prognostic Index

All Patients		**International; Index**[a]	
Age	> 60	Low Risk	0-1
Serum LDH	> normal	Low-Intermediate-risk	2
Performance Status	> 1	High-Intermediate-risk	3
Stage	III or IV	High-Risk	4 or 5
Extranodal involvement	> 1 site		

IPI = International Prognostic Index, LDH = Lactic acid dehydrogenase, NCCN-IPI = National Comprehensive Cancer Network- International Prognostic Index

[a] The international Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkins's lymphoma. N Engl J Med 1993; 329:987-994

Table 23: National Comprehensive Cancer Network- International Prognostic Index

NCCN-IPI (Zhou, 2014)			
Age, years		**Risk Group**	
> 40 to ≤ 60	1	Low	0-1
> 60 to < 75	2	Low-Intermediate	2-3
≥ 75	3	High-Intermediate	4-5
LDH, normalized (ratio to the institutional upper limit of normal)		High	≥ 6
> 1 to ≤ 3	1		
> 3	2		
Ann Arbor stage III-IV	1		
Extranodal disease in major organs: bone marrow, CNS, liver/GI tract, or lung	1		
Performance Status ≥ 2	1		

LDH = Lactic acid dehydrogenase, NCCN-IPI = National Comprehensive Cancer Network- International Prognostic Index

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: Wednesday, 30 October 2019, 11:06 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

The purpose of Protocol Amendment 4 is to close the study, discontinue the Follow-up Period, and stop data collection in the clinical database.

The protocol-defined primary analysis was completed with a data cutoff date of 02 Aug 2018, and the last subject's last durvalumab dose occurred on 04 Mar 2019. Subsequently, the last durvalumab subject's 90-day Safety Follow-up Visit was completed. At the time of the data cutoff date of the last 90-day Safety Follow-up Visit (06 Jun 2019), 30 subjects were in follow-up. No subjects were on treatment with durvalumab or any other study treatments.

There are no further plans to evaluate long-term efficacy, including overall survival, for the remaining subjects on study, and no additional statistical analysis on safety and efficacy will be performed.

Therefore, the Follow-up Period will be discontinued, and data collection in the clinical database will stop under this amendment. Subjects who received lenalidomide will continue to be followed for second primary malignancies (SPMs) as required by this study protocol (Section 3.1.3.1) [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 per protocol are no longer required to be followed for disease progression, subsequent anti-lymphoma therapy, and overall survival. Follow-up procedures, efficacy assessments, central labs, imaging, adverse events/serious adverse events (AEs/SAEs), and survival data collection can stop and will not be collected in the case report forms (CRFs).

Revised Sections: Protocol Summary, Section 1, Section 2, Section 3.1.3.2, Figure 1, Table 3, Section 6.3.3, Section 6.4.2, and Section 10.1.

- **Second Primary Malignancies (SPMs) data collection**

Collection and monitoring of SPMs will continue as events of interest and will be reported as SAEs for those who received lenalidomide. 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, reported as SAEs to Celgene Drug Safety and collected in the safety database. It is no longer required to collect SPMs in the clinical database, ie, AE and SPM CRFs.

Revised Section: Protocol Summary, Section 1, Section 2, and Section 10.7.2.1.

Other changes included in this amendment are summarized below:

- Editorial updates. – Protocol Summary, Table 4, Section 7, Section 7.2.5.2, and Section 9.1.
- Provided background, enrollment completion update, and purpose of protocol amendment 4. – Protocol Summary and Section 1.

- Specified no additional efficacy or safety analyses will be performed after the primary analysis (data cutoff date 02 Aug 2018). – Protocol Summary and Section 9.8.
- Any data generated after the last durvalumab subject's 90-day Safety Follow-up Visit (data cutoff date 06 Jun 2019) will be maintained in the source documents and not required to be entered in the clinical database. – Section 14.1 and Section 14.2.
- Removed Health Canada. Protocol was not opened for enrollment in Canada. – Section 15.2.

1. JUSTIFICATION FOR AMENDMENT

Protocol Amendment 3 is written to implement changes to the study as communicated in an investigator letter.to all participating sites on 16 Jan 2018. As announced, following the Partial Clinical Hold instituted by the United States (US) Food and Drug Administration (FDA) in September 2017, Celgene in collaboration with AstraZeneca/MedImmune has decided to modify this study to include a total sample size of approximately 40 subjects in the efficacy evaluable population and to change the study primary endpoint to the rate of subjects with Complete Response at the end of the induction therapy with durvalumab + rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP).

Significant changes included in this amendment are summarized below:

- Protocol Summary and Sections 3.1 (Study Design), 4.1 (Number of Subjects), 9.1 (Statistical Considerations – Overview) and 9.3 (Sample Size and Power Considerations): references to sample size have been updated to "*approximately 45 subjects are planned to be enrolled into this study (with approximately 40 subjects in the efficacy evaluable population.)"*
- Protocol Summary and Sections 2 (Study Objectives and Endpoints, Table 2: Study Endpoints), 3.1 (Study Design), 4.1 (Number of Subjects), 9.1 (Statistical Considerations – Overview), 9.3 (Sample Size and Power Considerations), 9.6 (Efficacy Analysis) and 9.9.3 (Exploratory Analysis): changes into the listed sections have been implemented to modify the primary endpoint to the complete response rate at the end of the induction therapy, to add as the key secondary endpoint the rate of subjects who continue consolidation therapy out of all subjects in the efficacy evaluable population and to move the progression-free survival (PFS) at 24 months from the primary to an exploratory endpoint in the study.

Other changes included in this amendment are summarized below:

- Protocol Section 2 (Study Objectives and Endpoints, Table 1), Section 3.1.2 (Treatment Period) and 7.2.3 (Study Drug Treatment): removed non-ABC DLBCL and ABC DLBCL as following the US FDA Partial Clinical Hold, all newly enrolled subjects are to be assigned to Arm A regardless of cell of origin (COO) diffuse large B-cell lymphoma (DLBCL), ABC or non-ABC subtype.
- Protocol Section 10.7.1 (AESIs for Durvalumab): the adverse events of special interest (AESIs) listed have been replaced by the following statement "*Further information on these AESIs (eg, presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure*."
- Correction of typographical errors and updated tables and table footnotes consistently with the revised text throughout the document.

1. JUSTIFICATION FOR AMENDMENT

Protocol Amendment 2 is written to address protocol deficiencies consequent to the Partial Clinical Hold instituted to this study by the United States (US) Food and Drug Administration (FDA) on 05 Sep 2017 and to include updates to Durvalumab Toxicity Management Guidelines as per Durvalumab Investigator's Brochure (IB) Edition 12, dated 03 Nov 2017.

Significant changes included in this amendment are summarized below.

- Protocol Summary and Section 1 (Introduction): Added the following statement to describe changes to the study following partial clinical hold placed by the US FDA: *"On 05 Sep 2017, a Partial Clinical Hold was placed to 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-programmed cell death-1 (PD-1) antibody, pembrolizumab, in patients with multiple myeloma in combination with immunomodulatory agents. Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) has been discontinued. This study will continue enrollment into Arm A. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who are receiving clinical benefit, based on the discretion of the investigator, may continue study treatment after being reconsented. Any newly enrolled subject after the US FDA Partial Clinical Hold will continue induction therapy on Arm A (durvalumab + R-CHOP) after Cycle 1 regardless of diffuse large B-cell lymphoma (DLBCL) cell of origin (COO) subtype."*
- Protocol Summary and Section 2 (Study objectives), Added as exploratory objective: *To evaluate impact on endpoints related to clinical activity of durvalumab when given in combination with R-CHOP followed by durvalumab consolidation."*
- Protocol Summary, Section 2 (Study objectives), Section 3.1 (Study Design), Section 6 (Procedures), section 7 (description of study treatments), Section 7.2.3.3 (Lenalidomide) and Section 9 (Statistical Considerations): Added as introductory statement and as footnote 1,2,3,6 and 7 for clarification: "*Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) has been discontinued. Subjects enrolled and treated in Arm B prior to the US FDA Partial Clinical Hold who are receiving clinical benefit, based on the discretion of the investigator, may continue study treatment after being reconsented. Any newly enrolled subject after the US FDA Partial Clinical Hold will continue induction therapy on Arm A (durvalumab + R-CHOP) after Cycle 1 regardless of DLBCL COO subtype."*
- Section 3.1.2 (Treatment Period), Figure 1 (Study Design) and section 7.2.3 (Study Drug Treatment): Added as statement and as footnotes into Figure 1: "*After the US FDA Partial Clinical Hold enrollment of new subjects into Arm B has been discontinued. If receiving clinical benefit at the discretion of the investigator, subjects may continue treatment in Arm B after being reconsented. Any newly enrolled subject with DLBCL of ABC COO subtype after the US FDA Partial Clinical Hold will continue induction therapy on Arm A after Cycle 1.*"

- Protocol Summary, Section 3.1 (Study Design), Section 6.5.1 (Safety Run-in Stage), Section 6.5.2 (Safety Review Committee) and Section 9.1 (Statistical Considerations Overview): Changes to the Safety run-in stage definition and addition of a statement for the Safety Run-in assessment of only Arm A: *"Following Partial Clinical Hold instituted by the US FDA which affects Arm B, the Safety Run-in Stage will evaluate safety of the treatment Arm A combinations when at least 10 subjects have been included into Arm A and have been treated for at least one cycle of study treatment or discontinued prematurely."*
- Protocol Summary and Section 9 (Statistical considerations): Clarifications added to statistical considerations as enrollment into Arm B has been discontinued. Sample size and power considerations reviewed following Partial Clinical Hold instituted by the US FDA with continuation of the study with all patients DLBCL ABC COO and non-ABC COO assigned to arm A.
- Section 1.3.1 (Durvalumab): Added information on new approval of durvalumab for the treatment of patients with locally advanced metastatic urothelial carcinoma.
- Section 1.4.2 (Rationale for Backbone Therapy (R-CHOP, R2-CHOP)): Added the following statement for clarification of changes in backbone therapy after US FDA Partial Clinical Hold: "*Following Partial Clinical Hold instituted by the US FDA rationale for backbone therapy has been changed. Any newly enrolled subject with ABC subtype will be treated with R-CHOP. Activated B-cell (ABC) subtype subjects already treated with R2-CHOP may continue study treatment if receiving clinical benefit, based on the discretion of the investigator and after being reconsented.*"
- Section 7.1.2 (Lenalidomide), Section 7.2.5.4 (Dose Modifications Guidelines for Lenalidomide) and 7.2.3.3 (Study treatment - lenalidomide): Added as clarification: "*No newly enrolled subjects are to be treated with the combination of durvalumab, R-CHOP plus lenalidomide. Only those subjects currently enrolled and receiving clinical benefit, based on the discretion of the investigator, are eligible to remain on treatment following reconsent.*"
- Section 7.2.5 (Dose Modifications (Interruption/Reduction)): Added for clarification in case of durvalumab dose hold "*If the requalification criteria are fulfilled, but the subject develops toxicity as described due to toxicities attributed durvalumab, R-CHOP should continue during the durvalumab dose hold.*"
- Section 7.2.5.2 (Dose Modification Guidelines for Durvalumab): Updates to the Dose Modification and Toxicity Management Guidelines as per the Durvalumab Toxicity Management Guidelines (TMGs) dated 01 Nov 2017: Updates implemented to Table 6 *(General Dose Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events)*, Table 7 (*Dose Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions*), Table 8 (*General Dose Modification and Toxicity Management Guidelines for Non-Immune-mediated Reactions*), Table 9 (*Dose Modification and Toxicity Management Guidelines for Non-Immune-mediated Adverse Events*) and Table 10 (*Dose Modification and Toxicity Management Guidelines for Infusion-Related Reactions*).

- Section 7.2.5.2 (Dose Modification Guidelines for Durvalumab), Table 6 (General Dose Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events) and Appendix A (Table of Abbreviations): the term imAE (immune-mediated adverse event) is replacing previous term irAE (immune-related adverse event).

1. JUSTIFICATION FOR AMENDMENT

[redacted] It is now noted in the protocol that, prior to beginning consolidation therapy with single-agent durvalumab, subjects who achieve only a partial response (PR) will be re-consented after initial induction therapy.

Updated Section(s):

Protocol Summary (Study Design), Section 3.1.2, Section 5 (Table of Events), Section 6.2.1, Section 7.2.3.1: Updated to specify subjects achieving a PR at end of induction may continue onto consolidation therapy based on the decision of the Investigator and after being re-consented for the consolidation treatment phase.

1. JUSTIFICATION FOR AMENDMENT

[redacted]

Significant changes included in the amendment are summarized below.

The following changes were made to the study protocol and the associated sections of the Protocol Summary:

- Section 4.2: Update of inclusion criterion 11 (c and d) for liver enzymes and hemoglobin.

  Rationale for change: *The laboratory entry criteria were tightened in order to reduce the risk for additive or synergistic toxicity of compounds of the study treatment.*

- Section 4.2: Update of inclusion criteria 12, 13 and 14 to:
  - Clarify highly effective methods for contraception,
  - Clarify timelines for subjects to abstain from breastfeeding, egg cell donation, blood and semen donation,
  - Clarify the requirement for subjects to understand and follow the overall lenalidomide standard pregnancy and counseling plan.
- Section 4.3: Update of exclusion criteria 8 and 9 to clarify that subjects known to be seropositive for hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are excluded.
- Sections 4.3 (exclusion criterion 23) and 8.2: Update of the duration of avoidance of use of live attenuated vaccines is from 30 days prior to the first dose of durvalumab, until 12 months after last dose of rituximab or until recovery of B-cells and for 120 days after last dose of durvalumab, whichever is longer.

  Rationale for change: *Live attenuated vaccines during and after study treatment should be avoided because the effects of the study backbone therapy, namely B-cell depletion by rituximab, and the PD-L1 inhibitor durvalumab, on such vaccination have not been evaluated. In order to not put study subjects at risk, live attenuated vaccines are not permitted during the defined periods of study participation and treatment.*

- Section 6 (Procedures): Clarification of the following assessments:
  - Safety run-in stage: Clarification by inserting a new section (6.5.1.).

- Safety review committee: Clarification by inserting a new section (6.5.2.).
- Pregnancy testing and lenalidomide counseling: Clarification following lenalidomide counseling document.

- Section 7.2 (Treatment Administration and Schedule):
  - Section 7.2.3.1. Criteria for stopping induction treatment and for starting consolidation treatment: Clarification of stopping criteria and rules.
  - Sections 7.2.3.5 and 8.1.6: Addition of special considerations regarding urinary tract toxicity of cyclophosphamide (hemorrhagic cystitis, pyelitis, ureteritis, hematuria).

    Rationale for change: Addition of specific details to support the risk-benefit assessment of the Investigator regarding cyclophosphamide as part of the R-CHOP backbone therapy in this study.

- Section 8:
  - Addition of information related to the Summary of Product Characteristics (SmPC) about lenalidomide interaction with digoxin, statins, and P-glycoprotein (P-gp) inhibitors.

    Rationale for change: Addition of specific details on drug-drug interactions related to lenalidomide to support the risk-benefit assessment of the Investigator.
  - Section 8.2 Prohibited Concomitant Medications and Procedures: Update to include information about risk of venous thromboembolism in subjects treated with lenalidomide in combination with dexamethasone, to note that combined oral contraceptive pills are not recommended in this clinical study and that Copper-releasing intrauterine devices are generally not recommended due to risks of infection.
  - Section 8.3.6. Hepatitis B virus reactivation prophylaxis as required (previously recommended). A hepatologist will be consulted and HBV DNA will be repeated in case of any elevation in liver enzymes of subjects who are treated with rituximab or lenalidomide. If liver enzymes are increased, a hepatologist should be consulted for further clarification (eg, hepatitis DNA PCR) and to decide on further treatment.

- Section 10 (Adverse Events):
  - Section 10.7.1 AESIs (adverse events of special interest) durvalumab: New section to define AESIs.
  - Section 10.7.2 AESIs lenalidomide: New section to define AESIs.

- Section 11 (Adverse Events): Addition of pregnancy as event for treatment discontinuation.

  Rationale for change: Addition of pregnancy as a specific reason for discontinuing treatment with investigational product.

In addition, some aspects of the original protocol version were clarified, spelling, formatting and punctuation errors were corrected, and various abbreviations and acronyms were spelled out. This amendment includes several other minor clarifications and corrections:

- Section 1.3.2: Addition of the US approval for lenalidomide for:
  - Maintenance multiple myeloma therapy following autologous hematopoietic stem cell transplantation
- Section 1.3.2: Addition of the EU approvals for lenalidomide for:
  - Maintenance treatment of newly diagnosed patients with MM who have undergone autologous stem cell transplantation,
  - Relapsed or refractory mantle-cell lymphoma (MCL).
- Section 1.4.5.2: Update of the rationale for Pd biomarker assay.
- Section 4.2: Update of inclusion criterion 8 to clarify that the on-treatment tumor biopsy is also required if clinically feasible in order to align with other sections of the study protocol.
- Section 4.2: Update of inclusion criterion 13 in order to align with the rituximab package insert or SmPC.
- Section 4.3: Update of exclusion criterion 4j to correct a spelling mistake (Burkitt's lymphoma).
- Section 4.3: Addition of exclusion criterion 26 ("prior organ transplantation including allogeneic stem cell transplantation").

  Rationale for change: Transplantation of allogeneic organs or stem cells resemble a medical condition that carries an increased risk for immune reactions including host-versus-graft and graft-versus-host reactions. In order to not put study subjects at risk, prior organ or allogeneic stem cell transplantation is not permitted.
- Section 5 (Table of Events): Revision of Table 3 (Schedule of Assessments) to update and clarify all assessment time points, particularly for PK and biomarkers.
- Section 6 (Procedures): Clarification of the following assessments:
  - Bone Marrow Biopsy: If screening FDG-PET demonstrates the bone marrow to be FDG-negative, no bone marrow biopsy (BMB)/aspirate is required.
  - Tumor Biopsy: Anonymized reports should be submitted, as well as locally stained slides.
  - Hepatitis B virus (HBV) serology to be assessed locally.
  - CT Scan schedule: It is also acceptable to perform the scans after that 50% of induction treatment was provided.
  - Bone Marrow biopsy and Aspirate: Samples not to be send to central laboratory.
  - Safety Assessments: Addition of NCI-CTCAE version 3.0 for TFR grading.

  - Pharmacokinetics: Addition of PK time points during induction therapy (C6D1, C8D1) and consolidation therapy (C4D1, C6D1, C8D1).
  - Biomarkers: Removal of the Aiolos and Ikaros sampling and analysis; Clarification and new timelines window for the tumor biopsies.

- Section 7.1 (Description of Investigational Products):
  - Section 7.1.1 (durvalumab): Update as per new IB version 10.
  - Section 7.1.3 (rituximab): Clarification that rituximab IV standard infusion time, rituximab IV generics and rituximab subcutaneous are acceptable.
- Section 7.2 (Treatment Administration and Schedule):
  - Section 7.2.2. Pre-specify Post-Induction Radiotherapy: Clarification that subjects with bulky disease are allowed to receive radiotherapy after induction treatment if planned before start of treatment.
  - Section 7.2.5.2: Update to Durvalumab Treatment Modification and Toxicity Management Guidelines (Table 6, Table 7, Table 8, Table 9, Table 10).
  - Section 7.2.3.1: Subjects achieving a PR at the end of the induction treatment may be allowed to continue with consolidation therapy with durvalumab if the Investigator considers this to be clinically justified.
- Section 9 (Statistical considerations): Several clarifications.