

DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

MEDI4736-DLBCL-001

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

The information contained in the attached report is the property of Celgene and should not be shared or used for any purpose other than that for which it was provided.

Celgene is committed to providing information about its clinical trials to researchers and patients with the goal of furthering science and enhancing healthcare worldwide. Laws and regulations require, however, that Celgene protect patient privacy. The company may further have legal or contractual obligations not to disclose commercial or technical information provided by or related to certain partner companies or vendors.

The attached report is presented in its original format, but certain information has been redacted in order to comply with the aforementioned obligations or to protect Celgene's confidential commercial information. The redactions are based on the following principles:

- Redacted information has been replaced by grey space, maintaining original spacing and pagination.
- Any information that might allow the identification of individuals has been redacted for anonymization.
- Attachments to this report that contain confidential information are not made available. Such attachments include those that contain identifiable patient information, such as subject listings, narratives, and profiles. They also may contain confidential commercial information such as methodologies, and hypothesis generating and exploratory analyses.
- Cross-references to these attachments (such as links to subject listings in Section 16.2) are not redacted from the body of the report. However, the hyperlinks in the electronic document are no longer functional.
- Information about Celgene vendors and their services are redacted because many contracts prohibit disclosure of that information. Further, laws and regulations prevent us from disclosing certain information about our vendors or their services because it is protected by copyright.

Information about Celgene's redaction policies and the availability of additional data from this report may be found at <http://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/>.

STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: MEDI4736 + R-CHOP or R2-CHOP
PROTOCOL NUMBER: MEDI4736-DLBCL-001
FINAL PROTOCOL DATE: 20 Jul 2016
AMENDMENT No. 1 DATE 09 May 2017
AMENDMENT No. 2 DATE 02 Jan 2018
AMENDMENT No. 3 DATE 27 Feb 2018

Prepared by:

CCI

On behalf of Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

CONFIDENTIAL

The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless such disclosure is required by law or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them

TABLE OF CONTENTS

SIGNATURE PAGE.....	7
1. LIST OF ABBREVIATIONS	8
2. INTRODUCTION.....	12
3. STUDY OBJECTIVES.....	13
3.1. Primary Objective.....	13
3.2. Secondary Objectives	13
CCI [REDACTED]	
4. INVESTIGATIONAL PLAN	14
4.1. Overall Study Design and Plan	14
4.2. Stratification, Randomization, and Blinding.....	19
4.3. Sample Size Determination.....	19
5. GENERAL STATISTICAL CONSIDERATIONS	20
5.1. Reporting Conventions	20
5.2. Analysis Populations	20
5.2.1. Safety Population.....	20
5.2.2. Efficacy Evaluable Population.....	21
CCI [REDACTED]	
5.2.4. Biomarker Evaluable Population.....	21
6. SUBJECT DISPOSITION.....	22
7. PROTOCOL DEVIATIONS/VIOLATIONS	23
8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS.....	24
8.1. Demographics.....	24
8.2. Baseline and Disease Characteristics.....	24
8.3. Medical History	24
8.4. Prior Cancer History	25
8.5. Prior and Concomitant Medications	25
8.5.1. Prior Medications	25
8.5.2. Concomitant Medications	25
8.5.3. Concomitant Procedures/Surgeries	25
9. STUDY TREATMENTS AND EXTENT OF EXPOSURE.....	26
9.1. Treatment Duration.....	26

9.2.	Cumulative Dose	28
9.3.	Dose Exposure.....	28
9.4.	Average Daily Dose.....	28
9.5.	Dose Intensity.....	28
9.6.	Relative Dose Intensity.....	28
9.7.	Dose Reduction/Interruption.....	29
10.	EFFICACY ANALYSIS	30
10.1.	Primary Efficacy Endpoint.....	30
10.2.	Key Secondary Endpoint	30
10.3.	Secondary Efficacy Endpoint.....	30
CCI	[REDACTED]	
10.5.	Subsequent Anti-Lymphoma Therapies	33
11.	SAFETY ANALYSIS	34
11.1.	Adverse Events.....	34
11.2.	Adverse Events of Special Interest.....	35
11.3.	Second Primary Malignancies.....	37
11.4.	Clinical Laboratory Evaluations.....	37
CCI	[REDACTED]	
11.6.	Vital Sign Measurements.....	38
11.7.	Physical Examination	38
11.8.	Electrocardiograms	38
11.9.	ECOG Performance Status.....	39
11.10.	B symptoms.....	39
CCI	[REDACTED]	
CCI	[REDACTED]	
CCI	[REDACTED]	
13.	INTERIM ANALYSIS	41
14.	CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL.....	42
15.	REFERENCES	43
16.	APPENDICES.....	44
16.1.	Handling of Dates.....	44
16.1.1.	Calculation Using Dates	44

16.1.2. Calculation of Cycles..... 45

16.2. Date Imputation Guideline..... 45

16.2.1. Impute Missing Adverse Events / Prior or Concomitant Medications 45

16.2.2. Medical History 46

16.2.3. Impute Missing Disease Diagnosis Dates..... 47

16.2.4. Impute Missing Dates in Prior Systemic Therapies 47

16.2.5. Impute Missing Dates in Subsequent Cancer Therapy..... 47

16.2.6. Impute Biomarkers 47

16.3. Recommendations for Initial Evaluation, Staging, and Response Assessment
of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification..... 48

LIST OF TABLES

Table 1:	Abbreviations and Specialist Terms	8
Table 2:	Study Endpoints	18
Table 3:	Number of Days to be Covered by the Last Dose	26
CCI	[REDACTED]	
[REDACTED]	[REDACTED]	
Table 6:	Criteria for Involvement of Site	48
Table 7:	Revised Criteria for Response Assessment.....	49
Table 7:	Revised Criteria for Response Assessment (continued).....	50

CELGENE PROPRIETARY INFORMATION

LIST OF FIGURES

Figure 1: Study Design 17

CELGENE PROPRIETARY INFORMATION

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	MEDI4736-DLBCL-001 Statistical Analysis Plan
SAP VERSION, DATE	Final Version 1.0, 16 August 2018
SAP AUTHOR	PPD
	Printed Name and Title Signature and Date
PROTOCOL 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
INVESTIGATIONAL PRODUCT	MEDI4736
PROTOCOL NUMBER	MEDI4736-DLBCL-001
PROTOCOL VERSION, DATE	Amendment 3, 27 Feb 2018
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.
Statistical Therapeutic Area Head	
Signature	_____
Printed Name	PPD _____ Date _____
Lead Clinical Research Physician / Clinical Research Physician	
Signature	_____
Printed Name	PPD _____ Date _____
Lead Product Safety Physician	
Signature	_____
Printed Name	PPD _____ Date _____

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ABC	Activated B-cell
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BE	Biomarker Evaluable
BSA	Body surface area
BLQ	below the limit of quantitation
C	Cycle
C1D1	Cycle 1 Day 1, first dose of treatment
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
COO	Cell of origin
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRR	Complete response rate
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
D	Day
DBP	Diastolic blood pressure
DI	Dose intensity
DLBCL	Diffuse large B-cell lymphoma
ECG	Electrocardiogram

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable
CCI	
FDA	Food and Drug Administration
GCB	Germinal center B-cell
GEP	Gene expression profiling
GRT	Global range table
HBV	Hepatitis B virus
ICF	Informed consent form
IHC	Immunohistochemistry
ILD	Interstitial lung disease
INR	International normalized ratio
IP	Investigational product
IPI	International Prognostic Index
IV	Intravenous
IWG	International Working Group
KM	Kaplan-Meier
LST	Lymphoma subtyping test
LVEF	Left ventricular ejection fraction
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MEDI4736	Durvalumab
Min	Minimum
n	Number
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
ORR	Overall response rate
OS	Overall Survival
CC	

Abbreviation or Specialist Term	Explanation
PD	Progressive disease

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand 1
PE	Pulmonary Embolism
PFS	Progression-free survival
CCI	
PR	Partial response
PS	Performance status
PT	Preferred term
PTT	Partial thromboplastin time
QD	Once daily
R2-CHOP	Lenalidomide plus R-CHOP
R-CHOP	Rituximab plus CHOP
RDI	Relative dose intensity
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SMQ	Standardized MedDRA Query
SOC	System organ class
SPM	Second primary malignancies
SRC	Safety Review Committee
StD	Standard deviation
TD	Translational development
TEAE	Treatment emergent adverse event
TFR	Tumor flare reaction
TLGs	Tables, listings, and graphs
US	United States
WHO	World Health Organization

Abbreviation or Specialist Term	Explanation
WHODD	WHO drug dictionary

CELGENE PROPRIETARY INFORMATION

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol MEDI4736-DLBCL-001 "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 (MEDI4736-DLBCL-001)" amendment #3 issued on 27 Feb 2018. The SAP contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy, safety and summary descriptive of pharmacokinetic concentrations. The statistical analysis of biomarker data will be the responsibility of Celgene Translational Development (TD) group.

This SAP describes the primary analysis which is conducted when the last patient has completed induction therapy, one CSR analysis at the timepoint when the last subject is followed-up for 24 months from the start of the study treatment and a final analysis at the time of study closure.

The full set of the tables, listings, and graphs (TLGs) will be used for the clinical study report (CSR). However, a subset of the TLGs will be generated from time to time for periodic review by the safety review committee (SRC). Additional ad hoc subgroup analyses may be performed as appropriate. All deviations from the SAP will be mentioned in the CSR. The report of the long-term second primary malignancy (SPM) is the responsibility of the sponsor.

Subjects will be assigned to one of the two treatment arms. Throughout this SAP, the treatment arms will be referred to as:

- Arm A: Durvalumab in combination with R-CHOP
- Arm B: Durvalumab in combination with R2-CHOP

The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to primary analysis. This SAP provides a description of the strategy, rationale, and statistical techniques to be used to achieve the objectives of the study. This SAP will be finalized and signed prior to the primary analysis. All statistical analyses detailed in this SAP will be conducted using Statistical Analysis System (SAS)[®] Version 9.3 or higher.

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 was discontinued following the Partial Clinical Hold. The study continued enrollment with all newly enrolled subjects being enrolled into Arm A and treated with durvalumab + R-CHOP regardless of diffuse large B-cell lymphoma (DLBCL) cell of origin (COO) subtype. The 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 with durvalumab + lenalidomide + R-CHOP after being reconsented.

3. STUDY OBJECTIVES

Primary, secondary ^{CCI} [REDACTED] objectives are mentioned in Section 3.1, Section 3.2 and Section 3.3. Please refer to Table 2 for the associated endpoints.

3.1. 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

3.2. 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 studies. Examples of defined analytical methods that will be investigated may include, but are not limited to:
 - Programmed cell death-ligand 1 (PD-L1) immunohistochemistry (IHC)
 - Gene expression signatures

^{CCI} [REDACTED]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

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 (Figure 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.

In this study, high-risk DLBCL is defined as meeting both

- (i) Ann Arbor Stage 3-4 or Ann Arbor Stage 2 with bulky disease (tumor diameter ≥ 7.0 cm), and
- (ii) Intermediate-high or high International Prognostic Index (IPI) risk ≥ 3 or National Comprehensive Cancer Network-IPI (NCCN-IPI) risk ≥ 4 .

Study Periods

The study consists of a Screening Period, a Treatment Period (induction and consolidation therapy), and a Follow-up Period.

Treatment Arms

All subjects at the start of Cycle 1 will be treated with durvalumab combined with R-CHOP during Cycle 1 of induction therapy.

Before the US FDA Partial Clinical Hold, subjects were assigned to receive one of the two induction therapies from cycle 2 onwards based on their DLBCL cell of origin (COO) subtype (ABC versus non-ABC) as determined by the NanoString Lymphoma subtyping test (LST) before start of cycle 2:

- *Arm A (non ABC subtype)*: 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 (ABC subtype)*: Durvalumab in combination with R2-CHOP^a

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 activated B-cell (ABC) subtype is identified prior to Cycle 1 Day 1 (C1D1).

^a : Enrollment into Arm B has been discontinued. This study will continue enrollment into Arm A only. 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

After the US FDA Partial Clinical Hold Enrollment into Arm B (durvalumab in combination with lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R2-CHOP]) was discontinued. Any newly enrolled subject was assigned to continue induction therapy on Arm A (durvalumab + R-CHOP) after Cycle 1, regardless of DLBCL COO subtype.

- **Consolidation Therapy (28-day cycles)**

Following induction therapy, subjects with complete response (CR) or partial response (PR), if it is considered a sufficient therapeutic response by the Investigator, will receive durvalumab consolidation therapy:

- *Arm A and Arm B*: Durvalumab

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.

Study Stages

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]) until at least 10 subjects are included in the *Safety Run-in*. Following Partial Clinical Hold instituted by the US FDA, the Safety Run-in Stage evaluates the safety of treatment Arm A when at least 10 subjects had been included into Arm A and had 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 the efficacy evaluable population. Following the US FDA Partial Clinical Hold, up to approximately 40 total subjects are anticipated 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, evaluated the safety profile of the Arm A treatment combinations during the *Safety Run-in Stage*. The decision to continue enrollment into the *Expansion Stage* occurred at the discretion of the sponsor following the evaluation of the *Safety Run-in Stage* by the SRC on December 19th, 2017.

Study Population

The study population will consist of previously untreated subjects with high-risk DLBCL.

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

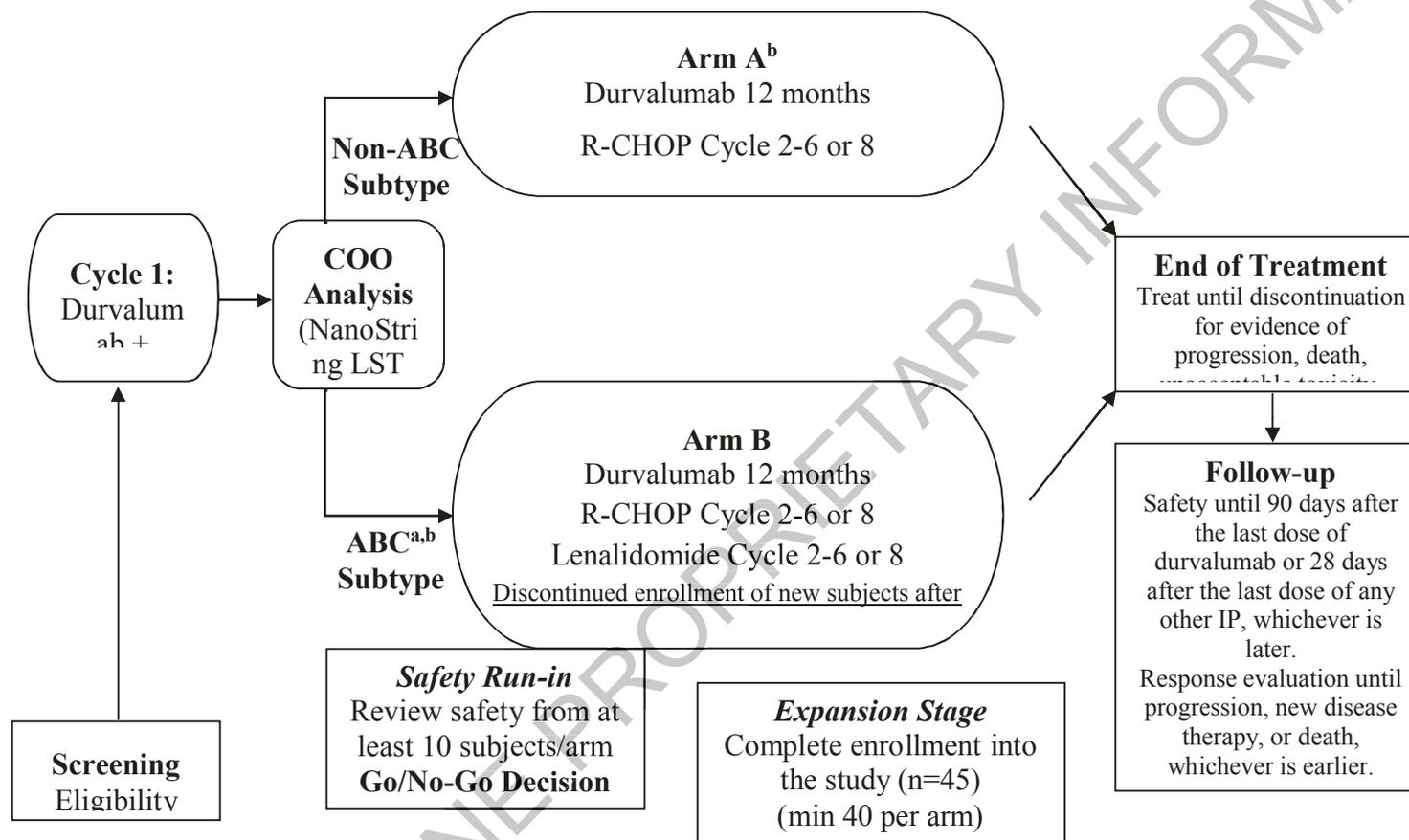
Study Duration for Subjects

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 for all subjects 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.

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

CELGENE PROPRIETARY INFORMATION

Figure 1: Study Design



Abbreviations: 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 was discontinued. If receiving clinical benefit at the discretion of the investigator, subjects could continue treatment in Arm B if being reconsented. Any newly enrolled subject with DLBCL of ABC COO subtype after US FDA Partial Clinical Hold continue induction therapy on Arm A after Induction Cycle 1, regardless of DLBCL COO subtype.

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 or 8 cycles (4 to 6 months) after the first dose of any IP
Key Secondary Endpoint			
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 or 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 during 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
CCI			

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
CCI			

Abbreviations: CR = complete response; CRR = complete response rate; IP = investigational product; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; CCI
 CCI
 ; TEAE = treatment emergent adverse events.

Source: Study protocol Table 2.

4.2. Stratification, Randomization, and Blinding

Not applicable.

4.3. Sample Size Determination

The total sample size for the study is estimated to be approximately 45 subjects. Assuming historical control data of 55% for the CRR at the end of the induction therapy in the efficacy evaluable population when treated with R-CHOP 75% for the CRR 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 CRR at the end of 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%.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

- Data from all study centers will be combined for analysis;
- All statistical tests of the treatment effect will preserve a significance level of 0.050 for 2-sided tests. Testing of interactions will be performed at the 0.100 significance level;
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999';
- Confidence intervals will be presented as 2-sided 95% CIs unless specified differently in specific analysis;
- Summary statistics will consist of the number and percentage of subjects (or cycles, if appropriate) in each category for discrete variables, and the sample size, mean, median, standard deviation (StD), minimum, and maximum for continuous variables;
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value;
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX.X%), where the percentage is in the parentheses;
- All listings will be sorted for presentation in order of treatment arm, study center, subject, and date of procedure or event;
- All analysis and summary tables will have the analysis population sample size (ie. number of subjects);
- The day of the first dose of study treatment, which may be administration of any of the study drugs included in the study treatment will be defined as C1D1;
- Baseline value will be defined as the last value on or before the first dose of study drug is administered; if multiple values are present for the same date and with no time information, the average of these values will be used as the baseline. For subjects who were not treated, the baseline will be the assessment value taken on the visit of C1D1 if available; otherwise, the value on or prior to enrollment date will be used.

5.2. Analysis Populations

5.2.1. Safety Population

The Safety Population will include all subjects who take at least one dose of IP. Subjects will be analyzed in the arm of the actual treatment received.

5.2.2. Efficacy Evaluable Population

The Efficacy Evaluable (EE) Population will include all subjects who complete at least one cycle of their assigned treatment, have a baseline assessment by computed tomography (CT) scan and have at least one post-baseline tumor response assessment. Subjects will be analyzed in the planned treatment arm regardless of the treatment received.

CCI [REDACTED]

5.2.4. Biomarker Evaluable Population

The Biomarker Evaluable (BE) Population will include all subjects who receive at least one dose of IP and have at least one post-dose biomarker assessment. Subjects will be analyzed in the arm of the actual treatment received.

6. SUBJECT DISPOSITION

The total number of subjects with screen failure will be summarized with reason for screening failure and listed. Enrollment by sites will be summarized by treatment arm for both periods, Treatment and Follow-up.

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for treatment discontinuation and study discontinuation) will be summarized using frequency and percent by arm for both periods, Treatment and Follow-up.

A summary of subject disposition will be presented by treatment arm for the following analysis populations:

- Safety Population;
- EE Population.

Reasons for treatment discontinuation will be collected on the case report form (CRF) and will be summarized for all enrolled subjects.

Reasons for study discontinuation will be summarized for all enrolled subjects.

Reasons for follow-up discontinuation will be collected on the CRF and will be summarized for all enrolled subjects who entered the follow-up phase.

A summary of subjects enrolled by site will be provided. Listings will be provided for subjects enrolled but not treated, and for discontinued subjects with reason for treatment discontinuation.

By-subject listing of subjects (with demographic and tumor type information included) will be provided with the following:

- Discontinuation (treatment and follow-up);
- Screen failure;
- Exclusion from the Safety, EE, CCI or BE Population.

7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations will be identified and assessed by the clinical research physician or designee following Celgene's standard operating procedures. The protocol deviations/violations will be summarized by treatment arm for the Safety Population.

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

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

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

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

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be carried out by treatment arm in the Safety Population and EE Population defined in Section 5.2. Listings will be presented for the Safety Population. Continuous variables will be summarized using descriptive statistics and categorical variables will be summarized with frequency counts and percentages.

8.1. Demographics

Age at time of consent (years), height (cm), weight (kg), body surface area (BSA, calculated using Dubois method) and other continuous demographic will be summarized using descriptive statistics (eg, mean, StD, median, minimum [Min] and maximum [Max]), while age categories (<50; ≥ 50 [years], < 65; ≥ 65 [years] and < 75; ≥ 75 [years]), race, sex, and other categorical variables will be summarized with frequency counts and percentages.

8.2. Baseline and Disease Characteristics

Baseline characteristics include temperature (°C), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), pulse (bpm), respiratory rate (breath per minute), Eastern Cooperative Oncology Group (ECOG) performance status (PS), Ann Arbor stage, left ventricular ejection fraction (LVEF), B symptoms (Present, Absent), hepatitis B virus (HBV) serology, and baseline electrocardiograms (ECGs) will be summarized.

Coagulation tests performed at screening will be summarized. Overall interpretation from coagulation test will be summarized along with prothrombin time, international normalized ratio (INR) and partial thromboplastin time (PTT or activated PTT)

Baseline laboratory assessments from central laboratory will be summarized for parameters listed in study protocol Section 6.1.

Creatinine clearance (CrCl) will be assessed at screening by the central laboratory. Creatinine clearance is estimated using the Cockcroft-Gault formula where

$$\text{CrCl (mL/min)} = (140 - \text{age [years]}) (\text{weight [kg]}) / (72 \times (\text{serum creatinine [mg/dL]}));$$

for females, the formula result is multiplied by 0.85 (15).

Disease characteristics at baseline (time from diagnosis of DLBCL to the date of first study treatment, Ann Arbor stage at diagnosis, presence of bulky disease, presence of B symptoms, molecular analysis and abnormalities, CD20 status of the tumor cells and extranodal involvements at baseline), will be summarized descriptively.

8.3. Medical History

A summary of medical and surgical history will be presented by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities® (MedDRA) Version 21.0, or higher. A similar summary will be generated for the currently active medical history only, by SOC and PT by treatment arm for Safety Population. Individual subject listings will be provided to support the summary tables.

8.4. Prior Cancer History

A summary of subjects with at least one prior cancer history will be presented by SOC and PT using MedDRA Version 21.0, or higher.

8.5. Prior and Concomitant Medications

The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization (WHO) (2016 version or higher) will be used to group medications into relevant categories. All prior medications will be summarized by ATC level 1 term, ATC level 4 term and preferred name in frequency tabulations by treatment arm for the Safety Population.

8.5.1. Prior Medications

Prior medications are defined as medications that were started before the first dose of the study treatment. A summary showing the number and percentage of subjects who took at least one prior medications will be presented by WHO therapeutic drug class and preferred name by treatment arm.

Listings of prior medications by subject will be provided.

8.5.2. Concomitant Medications

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

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

All concomitant treatments documented during the study will be summarized in frequency tabulations by arm for the Safety Population. The ATC coding scheme of the WHO Drug Enhanced 2016 version or higher will be used to group medications into relevant categories for these tabulations.

Listing of concomitant medications by subject will be provided.

8.5.3. Concomitant Procedures/Surgeries

The CRF page records procedure, date, and indication. These procedures will be coded using MedDRA Version 21.0 or higher. A summary table of subjects who had at least one concomitant procedure will be presented by SOC and preferred term by treatment arm for the Safety Population.

Concomitant procedures will be identified as procedures or surgeries that occurred after or on the date of signs the informed consent date, throughout the study and until 90 days after the last dose of durvalumab or 28 days after the last dose of any other IP, whichever is later.

Listing of concomitant procedures/surgeries by subject will be provided.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided based on the Safety and EE Populations. Descriptive statistics will be provided for treatment exposure and duration, cumulative dose, dose intensity (DI), and relative DI (RDI) by treatment arm. Individual subject listings will be provided to support the tables.

9.1. Treatment Duration

The treatment duration of durvalumab, lenalidomide, and R-CHOP will be summarized separately where R-CHOP is viewed as a combined regimen.

Imputations for the time of end of infusion might be considered after all efforts have been done to collect the data.

Treatment duration (weeks) for each study drug is defined as:

$$[(\text{study drug end date}) - (\text{date of Cycle 1 Day 1}) + 1] / 7$$

Study drugs end date is defined as Min [last non-zero/non-missing dose date + days to be covered by the last dose, death date].

The number of days to be covered by the last dose is defined in the [Table 3](#).

Table 3: Number of Days to be Covered by the Last Dose

Phase IP	Dose level	Schedule	n = days to be covered by the actual last dose (if schedule respected)	Change to apply for n if schedule is not respected
Induction (21 days per cycle)				
Durvalumab	1125 mg	Induction CxD1	n = 20	If durvalumab given later than D1 during induction Cx, i.e. at Dy, please modify days to be covered by actual last dose by n - (y - 1)
Rituximab	375 mg/m ²	Induction CxD1	n = 20	If rituximab given later than D1 during induction Cx, i.e. at Dy, please modify days to be covered by actual last dose by n - (y - 1)
Cyclophosphamide	750 mg/m ²	Induction CxD1	n = 20	If cyclophosphamide given later than D1 during induction Cx, i.e. at Dy, please modify days to be covered by actual last dose by n - (y - 1)

Table 3: Number of Days to be Covered by the Last Dose (Continued)

Phase IP	Dose level	Schedule	n = days to be covered by the actual last dose (if schedule respected)	Change to apply for n if schedule is not respected
Doxorubicin	50 mg/m ²	Induction CxD1	n = 20	If doxorubicin given later than D1 during induction Cx, i.e. at Dy, please modify days to be covered by actual last dose by n - (y - 1)
Vincristine	1.4 mg/m ² (up to 2.0 mg total)	Induction CxD1	n = 20	If vincristine given later than D1 during induction Cx, i.e. at Dy, please modify days to be covered by actual last dose by n - (y - 1)
Prednisone / Prednisolone	100 mg	Induction CxD1 to Induction CxD5	n = 16	If last dose date in induction Cx is earlier than D5, i.e. at Dy, please modify days to be covered by actual last dose by n + (5 - y) If last dose date in induction Cx is later than D5, i.e. at Dy, please modify days to be covered by actual last dose by n - (y - 5)
Lenalidomide	15 mg	Induction CxD1 to Induction CxD14	n = 7	If last dose date in induction Cx is earlier than D14, i.e. at Dy, please modify days to be covered by actual last dose by n + (14 - y) If last dose date in induction Cx is later than D14, i.e. at Dy, please modify days to be covered by actual last dose by n - (y - 14)
Consolidation (28 days per cycle)				
Durvalumab	1500 mg	Consolidation CxD1	n = 27	If durvalumab given later than D1 during consolidation Cx, i.e. at Dy, please modify days to be covered by actual last dose by n - (y - 1).

9.2. Cumulative Dose

The cumulative dose during treatment is defined as the sum of all doses taken across the Treatment Period for each study drug in mg (for durvalumab, lenalidomide, and prednisone/prednisolone), or in mg/m^2 (for rituximab, cyclophosphamide, doxorubicin, and vincristine). Since the planned durvalumab dose is different for the induction period and for the consolidation period, the cumulative dose will be separately summarized for the induction period and for the consolidation period.

9.3. Dose Exposure

Dose exposure (days) is defined as the total number of days on the particular drug during the treatment phase (excluding the periods of dose break per protocol or dose interruptions). Dose exposure will be calculated separately for each drug by treatment arm. For durvalumab, its dose exposure (days) will be separately summarized for induction period and for consolidation period.

9.4. Average Daily Dose

Average daily dose of a particular drug is defined as the cumulative dose divided by dose exposure, and expressed as mg/day or $[\text{mg}/\text{m}^2]/\text{day}$. Average dose will be calculated separately for each drug by treatment arm. For durvalumab, the average daily dose (mg/day) will be separately summarized for induction period and for consolidation period.

9.5. Dose Intensity

Dose intensity of a particular drug is defined as the cumulative dose per cycle and expressed as mg/cycle or $[\text{mg}/\text{m}^2]/\text{cycle}$. In general, it is calculated as cumulative dose divided by the planned number of cycles of the drug. The number of cycles of the drug is determined as the last cycle during which a subject received the drug regardless of the cycle being completed or discontinued. Dose intensity will be calculated for each drug separately by treatment arm. For durvalumab, its DI will be separately summarized for induction period and for consolidation period.

9.6. Relative Dose Intensity

Relative DI is defined as the actual DI divided by the planned DI*100.

During induction therapy (cycle length: 21 days), the planned DI for each IP are:

- Durvalumab: 1125 mg/cycle ;
- Rituximab: 375 $\text{mg}/\text{m}^2/\text{cycle}$;
- Cyclophosphamide: 750 $\text{mg}/\text{m}^2/\text{cycle}$;
- Doxorubicin: 50 $\text{mg}/\text{m}^2/\text{cycle}$;
- Vincristine: 1.4 $\text{mg}/\text{m}^2/\text{cycle}$ (up to 2 mg for obese or very tall subjects);
- Prednisone/prednisolone: 500 mg/cycle ;
- Lenalidomide (mg/day): 210 mg/cycle .

During consolidation therapy (cycle length: 28 days), the planned DI for durvalumab is:

- Durvalumab: 1500 mg/cycle.

Descriptive statistics of overall and by cycle RDI will be summarized. Additionally, the number and percentage of subjects will be summarized by category such as $\leq 85\%$ and $> 85\%$ for relative total DI of each study drug.

9.7. Dose Reduction/Interruption

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.

Dose reduction is defined as a nonzero dose administered after the C1D1 dose which is at a lower dose level than the dose the subject received at the previous dosing day.

Dose interruption occurs if the record of actual administered dose is zero except as required by the protocol. If an interruption happens at the start of cycle and causes the cycle to be postponed, it is called dose delay. Consecutive zeros are counted as one interruption.

Dose reduction or dose interruption will be summarized for vincristine and lenalidomide. The number of subjects who have at least one dose reduction (or interruption), time to first dose reduction (or interruption), number of subjects who had at least one dose reduction (or interruption) due to AE and time to first dose reduction (or interruption) due to AE will be provided.

A summary of subjects with delay in start of cycle and reason for delay will be summarized for durvalumab, R-CHOP and lenalidomide.

Dose interruption will be summarized for durvalumab and R-CHOP. Number of subjects who had at least one interruption, time to the first interruption, number of subjects who had at least one interruption due to AE and time to first interruption due to severe infusion (for drug administered by infusion) or allergic reactions, or other toxicities will be summarized. Number of subjects with at least one incomplete infusion (for drug administered by infusion) will be summarized.

10. EFFICACY ANALYSIS

All efficacy analyses will be carried out on the EE Population as well as on the Safety Population.

All efficacy endpoints will be summarized for each treatment arm by combining data from both the Safety Run-in Stage and the Expansion Stage.

All CIs will be provided at a level of 95%.

Efficacy subgroup analyses will be performed by DLBCL subtype (non-ABC classified as germinal center B-cell [GCB], unclassifiable and total non-ABC; ABC and Total), duration of induction therapy (6-cycle induction; 8-cycle induction), age categories (< 65; ≥ 65 [years]) and sex.

10.1. Primary Efficacy Endpoint

The study will test the hypothesis for the primary endpoint that CRR at the completion of induction therapy is above or on 55% against the null hypothesis that the CRR is below 55% at a 2-sided 5% level of significance, with a power estimated to be around 71%.

$$H_0: \text{CRR} < 55\% \text{ versus } H_1: \text{CRR} \geq 55\%.$$

The CRR will be summarized using count and percentage. The 95% 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 completion of the induction therapy in the efficacy evaluable population is above 55%.

10.2. Key Secondary Endpoint

The key secondary endpoint of this study is the rate of subjects who continue consolidation therapy out of all subjects.

The rate of subjects who continue consolidation therapy will be summarized using count and percentage. The 95% 2-sided confidence interval will be based on the Clopper-Pearson approach.

If null hypothesis for the primary endpoint is rejected, then hypothesis testing on the key secondary endpoint will be performed 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%.

10.3. Secondary Efficacy Endpoint

The secondary endpoint of this study is the identification of biomarkers which predict response. The statistical analysis of biomarker data and the evaluation of their predictive characteristics will be the responsibility of Celgene TD group. Many different potential biomarker

CCI



CCI

10.5. Subsequent Anti-Lymphoma Therapies

The subsequent antilymphoma therapies will be coded using WHO drug dictionary (WHODD) version 2016 or later. A frequency summary of subjects by antilymphoma therapies summarized in frequency tabulations by ATC level 1, ATC level 4 and drug preferred term by treatment arm for the Safety Population.

11. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study. All summaries of safety data will be conducted using the Safety Population. Descriptive statistics will be provided by treatment arm for all subjects combined (data from both the Safety Run-in Stage and the Expansion Stage).

11.1. Adverse Events

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

Adverse events will be coded according to the MedDRA Version 21.0 or higher. The intensity of AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher with the exception of the evaluation of tumor flare reaction (TFR) which will be graded according to NCI-CTCAE version 3.0. For all other AEs not described in the CTCAE criteria, the intensity will be assessed by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or death (Grade 5).

The incidence of TEAEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT). If a subject experiences the same AE more than once with a different toxicity grade, then the event with the highest grade will be tabulated in “by grade” tables. If a subject experiences multiple AEs under the same PT (resp. SOC), then the subject will be counted only once for that PT (resp. SOC). In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of “Missing” and will not be imputed.

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

Tables summarizing the incidence of TEAEs by treatment arm for all subjects combined will be generated with the following:

- All TEAEs;
- TEAEs by age group;
- TEAEs by sex;
- TEAEs related to durvalumab or any other IP;
- TEAEs by CTCAE Grade 3 or 4;
- TEAE related to durvalumab or any other IP with Grade 3 or 4;
- TEAEs with death outcome;
- TEAEs with death outcome related to durvalumab or any other IP;
- Serious TEAEs;
- Serious TEAEs related to durvalumab or any other IP;

- TEAEs leading to discontinuation of durvalumab or any other IP;
- TEAEs leading to interruption of durvalumab or any other IP;
- TEAEs leading to dose reduction of vincristine or lenalidomide;
- TEAEs by cycle of onset;
- TEAEs related to durvalumab or any other IP by cycle onset;
- TEAEs by maximum CTCAE grade;
- TEAEs related to durvalumab or any other IP by maximum CTCAE grade;
- Common ($\geq 10\%$) TEAEs;
- Common ($\geq 10\%$) TEAEs related to durvalumab or any other IP.

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

All deaths, on treatment deaths, off treatment deaths and causes of death will be summarized. Deaths within 90 days after the last dose of durvalumab or 28 days after last dose of any other IP will be summarized separately.

Individual subject listing of AEs will be presented. In addition, tabulated lists will be provided with the following:

- Serious TEAEs;
- TEAEs leading to permanent withdrawal of any study drug;
- Subjects who died.

11.2. Adverse Events of Special Interest

The adverse events of special interest (AESI) refer to a group of terms/PTs from one or more SOCs relating to a defined medical condition or area of interest. The AE of special interest phrase or term refers to the group of PTs, rather than the individual PTs. The AESI will be searched using the Standardized MedDRA Query (SMQ), Sub-SMQ search criteria or a collection of selected ad-hoc PTs used to define and monitor the AESI.

The following durvalumab AESIs, as identified by AstraZeneca/MedImmune, will be summarized and listed:

- Adrenal insufficiency;
- Colitis;
- Diarrhoea;
- Guillain-Barre syndrome;
- Hepatic laboratory parameters reported as AEs;
- Hepatitis;

- Hypersensitivity/Anaphylactic reactions;
- Hyperthyroidism;
- Hypophysitis;
- Hypothyroidism;
- Infusion related reaction;
- Intestinal perforation;
- Myasthenia gravis;
- Myocarditis;
- Myositis;
- Nephritis;
- Other rare/miscellaneous (including other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology);
- Pancreatic laboratory investigations reported as AEs;
- Pancreatitis;
- Pneumonitis;
- Rash/Dermatitis;
- Renal laboratory investigations reported as AEs;
- Thyroid laboratory parameters reported as AEs (decreased thyroid activity);
- Thyroid laboratory parameters reported as AEs (increased thyroid activity);
- Thyroiditis;
- Type 1 diabetes mellitus.

This list might be updated after the SAP signature and the analysis will reflect the most updated list to evaluate accurately the safety.

The following lenalidomide AESI will also be summarized and listed for subjects in Arm B who received lenalidomide:

- Cardiac arrhythmias;
- Cardiac failure;
- Infection;
- Invasive-AML/ B-cell malignancies/Cumulative/Other haematologic malignancies/Solid Tumors-Cumulative;

- Invasive-SPM Hematologic Malignancies/SPM Solid Tumor- Renal and Urinary/SPM Solid Tumor- Reproductive/SPM Solid Tumors-Breast/SPM Solid Tumors-Endocrine/SPM Solid Tumors-Gastrointestinal/SPM Solid Tumors-Hepatobiliary/SPM Solid Tumor-Skin/SPM Solid Tumors-Mesotheliomas/SPM Solid Tumors-Miscellaneous/SPM Solid Tumors-Nervous System/SPM Solid Tumors-Ocular/SPM Solid Tumor-Soft Tissue/SPM Solid Tumors-Skeletal;
- Ischaemic Heart Disease (including myocardial infarction);
- Neutropenia;
- Non-invasive-SPM: Non-Invasive Skin Cancers;
- Teratogenicity;
- Tumour Flare Reaction;
- Unspecified.

Standard MedDRA query search list will be saved as appropriate for each tables, listings and figures delivery.

11.3. Second Primary Malignancies

Second primary malignancies will be collected at any time from the time of signing the ICF 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 AESI.

Listings for the SPM events will be provided.

11.4. Clinical Laboratory Evaluations

Descriptive statistics (n, Mean, StD, median, Min, and Max) of observed and change from baseline values will be presented by treatment arm.

Clinical laboratory values will be graded according to CTCAE Version 4.03 or higher for applicable tests. Baseline grade and worst grade during treatment for selected laboratory results will be summarized. Shifts from baseline to the worst grade observed during the treatment for selected laboratory results will also be provided. Normal ranges will be used to determine the categories of High, Low, and Normal for lab tests that have no severity grade. Normal ranges from Celgene's global range table (GRT) will be used for local laboratory data.

Listings of clinical laboratory data from central laboratory with abnormal flags will be provided by subjects and tests. Listings will also be provided for the local laboratory data.

CCI

11.6. Vital Sign Measurements

For vital signs with shifts from baseline to worst during treatment (below, within, and above the normal ranges) will be displayed in cross-tabulations. Summary statistics (n, Mean, StD, median, Min, and Max) of observed and change from baseline values will be presented.

Normal ranges are defined as follows:

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

The worst value will be defined as follow:

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

11.7. Physical Examination

Physical examination includes evaluation of lymph nodes, neurological status, internal organs and skin. Physical examination findings will be summarized in frequency tables by body systems and treatment arm for all subjects combined.

11.8. Electrocardiograms

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with 'Normal', 'Abnormal, not clinically significant', and 'Abnormal, clinically significant' by treatment. The shift from baseline to worst during the treatment in the overall ECG interpretation will be displayed in cross-tabulations for each treatment.

11.9. ECOG Performance Status

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

11.10. B symptoms

Description of subjects with B symptoms will be listed per arm.

CELGENE PROPRIETARY INFORMATION

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CELGENE PROPRIETARY INFORMATION

13. INTERIM ANALYSIS

Not applicable.

CELGENE PROPRIETARY INFORMATION

14. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

The primary endpoint changes from PFS at 24 months to CRR at induction completion compared to the original protocol. The timing of the primary analysis has changed to be at the induction completion, the CSR analysis will be conducted at the end of 24months follow up (original timing of the primary analysis) and the final analysis will be done at study closure

After the US FDA Partial Clinical Hold enrollment of new subjects into Arm B was discontinued. Any newly enrolled subject with DLBCL of ABC COO subtype after US FDA Partial Clinical Hold continue induction therapy on Arm A after Induction Cycle 1, regardless of DLBCL COO subtype. Therefore, descriptive analysis will be conducted in arm B however no conclusion will be drawn due to the limited number of subjects.

15. REFERENCES

- CCI [REDACTED]
- (FDA) Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. FDA/CDER/CBER; May 2007.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
- Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano Classification. *J Clin Oncol* 2014;32(27):3059-68.

16. APPENDICES

16.1. Handling of Dates

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

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 16.2 (eg, for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

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

16.1.1. Calculation Using Dates

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

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug (eg, lenalidomide) plus 1 day. The generalized calculation algorithm for relative day is the following:
 - If TARGET DATE \geq DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;

- Else use $\text{STUDY DAY} = \text{TARGET DATE} - \text{DSTART}$.

Note that Study Day 1 is the first day of treatment of study drug. Negative study days are reflective of observations obtained during the baseline/Screening period. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.

- Age (expressed in days) is calculated: $\text{AGE} = \text{CONSENT} - \text{DATE of BIRTH} + 1$. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
 - Preference is for using calculated age from clinical database. When not available, calculated age from CRF or Interactive Voice Response System (IVRS) may be used
 - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

$$\text{WEEKS} = \text{DAYS} / 7$$

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

$$\text{MONTHS} = \text{DAYS} / 30.4167$$

16.1.2. Calculation of Cycles

The cycle information will be captured on the eCRFs.

16.2. Date Imputation Guideline

16.2.1. Impute Missing Adverse Events / Prior or Concomitant Medications

Incomplete Start Date:

Missing day and month

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

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.

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

Missing day, month, and year

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

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

Missing day and month

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

Missing day only

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

16.2.2. Medical History

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

the day missing, and July 1st will be used to impute a partially missing start date that has both the month and day missing.

16.2.3. Impute Missing Disease Diagnosis Dates

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

16.2.4. Impute Missing Dates in Prior Systemic Therapies

For each prior systemic therapy, if the day of any date is missing, then the first day the non-missing month will be assigned to the missing day; if month or year of the date is missing, the date will not be imputed and treated as missing.

16.2.5. Impute Missing Dates in Subsequent Cancer Therapy

Patient will be allowed to take other cancer therapy after discontinued from the study. The lymphoma therapy start/stop date will be collected. If the day of any date is missing, then the last day the non-missing month will be assigned to the missing day; if day and month are both missing, then the December 31 of the non-missing year will be assigned to the missing day. Any imputed dates should be before the death date, if not death date will be used instead.

The progression date should not be imputed.

16.2.6. Impute Biomarkers

For each biomarker test, if the values are below the lower or above the upper limit of quantification, then the values are imputed to the respective limit of quantification (lower or upper). Summary statistics will not be provided in case more than 40% of the values are imputed.

16.3. 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 6: 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 uptake, solitary mass, military lesions, nodules > 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies Nonavid disease	PET-CT CT	Diffuse uptake, mass Nodules
CNS	Signs, symptoms		CT MRI CSF assessment	Mass lesion(s) Leptomeningeal infiltration, mass lesions Cytology, flow cytometry
Other (eg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT ^a , biopsy	Lymphoma involvement

Abbreviations: CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; MRI = magnetic resonance imaging; PET = positron emission tomography.

^a For determination of bone marrow involvement, PET-CT is adequate and it can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Source: Cheson, 2014.

Table 7: 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 8: 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	Score 4 or 5 ^b with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the 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

Table 7: Revised Criteria for Response Assessment (continued)

Response and site	PET-CT based response	CT-based response
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis, if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

^a A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where 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: 15.



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: PPD [REDACTED]
Title: PPD [REDACTED]
Date: Friday, 24 August 2018, 10:55 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
=====

UserName: PPD [REDACTED]
Title: PPD [REDACTED]
Date: Friday, 24 August 2018, 11:06 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
=====

UserName: PPD [REDACTED]
Title: PPD [REDACTED]
Date: Monday, 27 August 2018, 04:07 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
=====

CELGENE PROPRIETARY INFORMATION