Protocol Number: ADCT-402-104

Official Title: A Phase 1 Open-Label Study to Evaluate the Safety and Antitumor Activity of Loncastuximab Tesirine and Durvalumab in Patients with Advanced Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, or Follicular Lymphoma

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CLINICAL STUDY PROTOCOL

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A Phase 1 Open-Label Study to Evaluate the Safety and Antitumor Activity of Loncastuximab Tesirine and Durvalumab in Patients with Advanced Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, or Follicular Lymphoma

PROTOCOL NO.: ADCT-402-104

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Date of Original Protocol: 1-August-2018
Protocol Amendment 1: 14-January-2019

Confidentiality Statement

Protocol Approval – Sponsor Signatory

Study Title:	A Phase 1 Open-Label Study to Evaluate the Safety and Antitumor Activity of Loncastuximab Tesirine and Durvalumab in Patients with Advanced Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, or Follicular Lymphoma
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Protocol Amendment 1:	14-January-2019

Protocol accepted and approved by:

[redacted]
Head of US Oncology Clinical Development
ADC Therapeutics America Inc.
[redacted]

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled: "A Phase 1 Open-Label Study to Evaluate the Safety and Antitumor Activity of Loncastuximab Tesirine and Durvalumab in Patients with Advanced Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, or Follicular Lymphoma" and the accompanying Investigator's Brochures (IB).

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the protocol amendment 1, dated 14-January-2019, the current version of International Council for Harmonisation (ICH) harmonised tripartite guideline E6: Good Clinical Practice, and all applicable governmental regulations. I will not make changes to the protocol before consulting with ADC Therapeutics or implement protocol changes without Independent Ethics Committee approval except to eliminate an immediate risk to patients. I agree to administer the study drugs only to patients under my personal supervision or the supervision of a sub-Investigator.

I will not supply the study drugs to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ADC Therapeutics SA.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

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List of Abbreviations

Abbreviation	Definition
ABW	adjusted body weight
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADR	adverse drug reaction
AE	adverse event
AI	accumulation index
Ala	alanine
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AlloSCT	allogeneic stem cell transplant
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{0-last}	area under the concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0-\tau}$	area under the concentration-time curve from time zero to the end of the dosing interval
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
BOR	best overall response
C	cycle
CAR	chimeric antigen receptor
CD	cluster of differentiation
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CRR	complete response rate
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	day
DESC	Dose Escalation Steering Committee
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Definition
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FL	follicular lymphoma
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HBV	hepatitis B virus
HCV	hepatitis C virus
HD-ASCT	high-dose chemotherapy and autologous stem cell transplant
HIV	human immunodeficiency virus
hr	hour
IB	Investigator's Brochure
IC	immune cells
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
ILD	interstitial lung disease
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
LFT	liver function test
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
MSD-ECL	Meso-Scale Discovery Electrochemiluminescence
MTD	maximum tolerated dose
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PBD	pyrrolobenzodiazepine
PD	progressive disease
PET	positron emission tomography
PET-CT	positron emission tomography - computed tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per os
pp	predicted probability
PR	partial response
PTT	partial thromboplastin time
QT	measure between Q wave and T wave in the electrocardiogram

Abbreviation	Definition
QTcF	Fridericia correction of the QT measure
Q3W	every 3 weeks
Q4W	every 4 weeks
RBC	red blood cell
RFS	relapse-free survival
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
SD	stable disease
SOC	system organ class
SoE	Schedule of Events
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
µL	microliter
ULN	upper limit of normal
US	United States
Val	valine
WBC	white blood cell
WHO	World Health Organization
wk	week
WOCBP	women of childbearing potential

Overall Summary and Rationale for Changes

Protocol Amendment 1

- Section 3 [redacted]
- Section 5.1 Inclusion criterion 8d was modified to remove exception to ALT, AST, and GGT criteria in patients with liver involvement to align with requirement to hold study drug for Grade ≥2 LFT increases
- Section 5.2 Exclusion criterion 18 was modified to remove the exception regarding patients with prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 therapy as patients who have received these therapies are excluded in exclusion criterion 2
- Section 6.4.3 Dose Limiting Toxicity Definition was modified to clarify the non-hematologic DLT definition
- Section 6.7.1 Premedication and Section 6.7.3 Treatment and Prophylaxis of Infusion-related Hypersensitivity Reactions were modified to allow the use of IV dexamethasone
- Section 9.8.1 Adverse Events was modified to align with the reporting period specified in in Section 8.2.2 Eliciting and Reporting Adverse Events/Serious Adverse Events
- Section 13.3 (Appendix 3) was modified to remove information related to management of toxicities in patients with hepatocellular carcinoma as no patients with hepatocellular carcinoma will be enrolled in the study
- Protocol synopsis was revised to align with the changes in the protocol
- Editorial corrections and clarifications were applied throughout

Protocol Synopsis

Protocol Number:	ADCT-402-104
Title:	A Phase 1 Open-Label Study to Evaluate the Safety and Antitumor Activity of Loncastuximab Tesirine and Durvalumab in Patients with Advanced Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, or Follicular Lymphoma
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 1b
Indication:	Diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL)
Rationale:	Non-Hodgkin lymphoma (NHL) is the 7th most common type of cancer in the U.S. and accounted for an estimated 4.3% of new cancer cases in 2017. It is most commonly a disease of older individuals with approximately 75% of new cases diagnosed in individuals 55 years of age or older (median age at diagnosis = 66 years). Response to initial treatment generally exceeds 50% and the overall 5-year survival rate in the U.S. is 70%. However, a significant proportion of patients will relapse. The poor prognosis for relapsed patients, especially those with chemotherapy-refractory disease with a short interval between remission and relapse, or those who relapse after high-dose therapy and autologous stem cell transplant (ASCT), highlights the need for new forms of treatment for NHL. Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate (ADC) directed against human cluster of differentiation 19 (CD19) that is well tolerated and has shown activity in patients with relapsed or refractory B-cell NHL in a Phase 1 study. It is anticipated to become a component of combination therapies that increase the response rate and durability of treatment. Checkpoint activation is an immune-evasion strategy that is operative in various tumors, both solid and hematological. There is pre-clinical evidence suggesting that the combination of an antibody-drug conjugate (ADC) and a checkpoint inhibitor (such as a PD-L1 blocker) may be more potent than either of the respective monotherapies (Müller et al., 2015). Early results from clinical trials combining ADCs and checkpoint inhibitors show potential increased effectiveness of the combination (Diefenbach et al., 2015; Diefenbach et al., 2016).

The primary purpose of this study is to explore whether loncastuximab tesirine and durvalumab can be safely combined, and if so, identify the dose(s) and regimens appropriate for further study. In addition, the study will potentially generate preliminary evidence as to whether loncastuximab tesirine combined with durvalumab may increase the response rate and durability of response compared to previous results with either compound as a single agent.

Objectives:

Primary Objective

- To characterize the safety and tolerability of loncastuximab tesirine in combination with durvalumab, and to identify the recommended dose and schedule for future studies

Secondary Objectives

- To evaluate the antitumor effect of the combination of loncastuximab tesirine with durvalumab
- To characterize the pharmacokinetic (PK) profile of loncastuximab tesirine when given in combination with durvalumab
- To evaluate the immunogenicity of loncastuximab tesirine when given in combination with durvalumab

[redacted]

Endpoints:

Primary Endpoints

- Frequency and severity of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of dose limiting toxicities (DLTs) during the 21 days after the first durvalumab dose (dose escalation only)
- Frequency of dose interruptions and dose reductions
- Changes from baseline of safety laboratory values, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs)

Secondary Endpoints

- Overall response rate (ORR) according to the 2014 Lugano classification as determined by the Investigator. ORR is the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR)
- Duration of response (DOR) defined as the time from the documentation of first tumor response to disease progression or death
- CR rate defined as the percentage of patients with a BOR of CR
- Relapse-free survival (RFS) defined as the time from the documentation of CR to disease progression or death
- Progression-free survival (PFS) defined as the time between start of treatment and the first documentation of recurrence, progression, or death
- Overall survival (OS) defined as the time between the start of treatment and death from any cause
- Concentrations and PK parameters of loncastuximab tesirine (total antibody, PBD-conjugated antibody, and unconjugated cytotoxin SG3199)
- Anti-drug antibody (ADA) titers and, if applicable, neutralizing activity to loncastuximab tesirine

[redacted]

Study Design:

This is a Phase 1b, open-label, single-arm combination study with a dose escalation phase (Part 1) followed by a dose expansion phase (Part 2). The study will enroll approximately 75 patients.

A standard 3+3 dose escalation design will be used. The DLT period will be the 21 days after the first durvalumab dose.

The dose expansion phase (Part 2) will consist of 3 cohorts of approximately 20 patients each, one for DLBCL, one for MCL, and one for FL, to obtain additional safety and preliminary antitumor activity information at the maximum tolerated dose (MTD)/RDE.

A Dose Escalation Steering Committee (DESC), composed of study investigators and ADC Therapeutics personnel, will be responsible for decisions concerning dose escalation.

Patient Selection:

Inclusion criteria:

1. Male or female patient aged 18 years or older
2. Pathologic diagnosis of DLBCL, MCL, or FL
3. Patients must have relapsed or refractory disease and have failed or been intolerant to standard therapy
4. Patients who have received previous CD19-directed therapy must have a biopsy that shows CD19 expression after completion of the CD19-directed therapy
5. Measurable disease as defined by the 2014 Lugano Classification
6. Patients must be willing to undergo tumor biopsy
7. ECOG performance status 0-1
8. Screening laboratory values within the following parameters:
   a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu L$ (off growth factors at least 72 hours)
   b. Platelet count $\geq 75 \times 10^3/\mu L$ without transfusion in the past 7 days
   c. Hemoglobin ≥9.0 g/dL (5.59 mmol/L), transfusion allowed
   d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) ≤2.5 × the upper limit of normal (ULN)
   e. Total bilirubin ≤1.5 × ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 × ULN)
   f. Blood creatinine ≤1.5 × ULN or calculated creatinine clearance ≥60 mL/min by the Cockcroft - Gault equation

   Note: A laboratory assessment may be repeated a maximum of two times during the Screening period to confirm eligibility.
9. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test within 3 days prior to start of study drug on C1D1 for women of childbearing potential
10. Women of childbearing potential must agree to use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of study therapy. Men with female partners who are of childbearing potential must agree that they will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of study therapy.

Exclusion criteria:

1. Known history of hypersensitivity to or positive serum human ADA to a CD19 antibody.
2. Previous therapy with any checkpoint inhibitor
3. Autologous stem cell transplant within 100 days prior to start of study drug (C1D1)
4. History of allogenic stem cell transplant
5. History of solid organ transplant
6. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:
   a. Patients with vitiligo or alopecia
   b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
   c. Any chronic skin condition that does not require systemic therapy
   d. Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician
   e. Patients with celiac disease controlled by diet alone
7. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice)
8. Known seropositive and requiring anti-viral therapy for human immunodeficiency (HIV) virus, hepatitis B virus (HBV), or hepatitis C virus (HCV)
9. History of Stevens-Johnson syndrome or toxic epidermal necrolysis
10. Lymphoma with active central nervous system (CNS) involvement at the time of screening, including leptomeningeal disease
11. Clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath)
12. Breastfeeding or pregnant
13. Significant medical comorbidities, including but not limited to, uncontrolled hypertension (blood pressure [BP] ≥160/100 mmHg repeatedly), unstable angina, congestive heart failure

(greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 6 months prior to screening, uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, or severe chronic pulmonary disease

14. Radiotherapy, chemotherapy, or other anti-neoplastic therapy within 14 days prior to start of study drug (C1D1), except shorter if approved by the Sponsor.
15. Major surgery within 28 days prior to start of study drug (C1D1), except shorter if approved by the Sponsor. Note: Local surgery of isolated lesions for palliative intent is acceptable.
16. Use of any other experimental medication within 14 days prior to start of study drug (C1D1)
17. Planned live vaccine administration after starting study drug (C1D1)
18. Failure to recover to Grade ≤1 (Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) from acute non-hematologic toxicity (Grade ≤2 neuropathy or alopecia) due to previous therapy prior to screening..
19. Congenital long QT syndrome or a corrected QTcF interval of >470 ms at screening (unless secondary to pacemaker or bundle branch block)
20. History of another primary malignancy except for:
    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of investigational product and of low potential risk for recurrence
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c. Adequately treated carcinoma in situ without evidence of disease
21. History of active primary immunodeficiency
22. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgement, make the patient inappropriate for study participation or put the patient at risk.

Estimated Duration of Patient Participation and Study Duration:

The duration of the study participation for each patient is defined as the time from the date of signed written informed consent to the completion of the follow-up period, withdrawal of consent, loss to follow-up, or death, whichever occurs first.

The study will include a Screening Period (of up to 28 days), a Treatment Period (cycles of 3, 6, and 4 weeks), and a Follow-up Period (approximately every 12 week visits for up to 2 years after treatment discontinuation).

Patients may continue treatment for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first.

The end of study occurs at the last visit or last scheduled procedure for the last patient, unless the study is terminated earlier by Sponsor.

Efficacy Assessments:

- Disease assessments: Positron emission tomography-computed tomography (PET-CT)

  Note: If disease is not PET avid at baseline, CT with contrast or magnetic resonance imaging (MRI) may be used for follow-up disease assessments.

  The assessment method determined to identify sites of disease at baseline should be used for all subsequent assessments.

Safety Assessments:

- Physical examination
- ECOG Performance status
- Height and weight
- Vital signs
- Safety laboratories (hematology, chemistry, coagulation, urinalysis, etc.)
- Pregnancy test, if applicable
- 12 Lead-ECG (triplicate)
- AEs/SAEs, graded according to CTCAE v4.0 (or more recent)

Other Assessments:

- Blood sampling for PK, ADA
- [redacted]

Study Drugs, Dosage, and Mode of Administration:

The dose of loncastuximab tesirine for patients treated at each dose level in Part 1 is shown below. Durvalumab will be administered every 4 weeks starting 1 week after the first dose of loncastuximab tesirine. The DLT evaluation period will be the 21 days after the first durvalumab dose.

Loncastuximab Tesirine Dose Escalation

Dose Level	Loncastuximab tesirine	Durvalumab
1	90 μg/kg IV on Day 1 Q3W × 2	1500 mg IV Q4W
2	120 μg/kg IV on Day 1 Q3W × 2	1500 mg IV Q4W
3	150 μg/kg IV on Day 1 Q3W × 2	1500 mg IV Q4W

Patients who have a response of PR or SD at the 15 week assessment may receive 2 additional doses of loncastuximab tesirine given 4 weeks apart.

Patients treated in Part 2 will receive study drugs at the dose and schedule determined in Part 1.

Sample Size:	Approximately 75 patients.
Statistical Considerations:	Safety analyses will be presented descriptively. Primary antitumor activity analyses will be based on response as determined by the Investigator. ORR and CR rate with 95% CI will be presented. DOR, PFS, RFS, and OS will be analyzed using the Kaplan-Meier approach.

Schedule of Events

Table 1 Schedule of Events

	Protocol Section	Screening	Treatment Period								Follow-up Period (up to 2 years from EOT)
			Cycle 1 (3 week cycle)			Cycle 2 (6 week cycle)[9]			Cycle 3 and beyond (4 week cycles)	EOT	Every 12 weeks
Day (D)		**-28 to –1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Informed consent	11.3	X									
Eligibility criteria	5	X									
Demography	9.5	X									
Medical/cancer history	9.5	X									
Tumor biopsy	8.5.1	X[1]									
Physical examination	8.3.1	X	X			X			X	X	
ECOG performance status	8.3.2	X	X			X			X	X	
Height	8.3.3	X									
Weight	8.3.3	X	X	X	X	X	X	X	X	X	
Vital signs (BP, HR, RR, Temp)	8.3.4	X	X	X	X	X	X	X	X	X	
Disease assessment[2]	8.1	X	6 weeks and 15 weeks after C1D1, then every 8 weeks							X[3]	Every 12 weeks until 1 year from EOT, then every 6 months until disease progression up to 2 years from EOT
Hematology and Chemistry	8.3.5	X	X[4]	X		X[4]	X		X	X	
Coagulation and Urinalysis	8.3.5	X									
TSH (reflex free T3 or free T4)	8.3.5	X	X			X			X	X	
Hepatitis B, C, and HIV tests	8.3.5	X									

	Protocol Section	Screening	Treatment Period							EOT	Follow-up Period (up to 2 years from EOT)
			Cycle 1 (3 week cycle)			Cycle 2 (6 week cycle)[9]			Cycle 3 and beyond (4 week cycles)		Every 12 weeks
Day (D)		**-28 to –1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Pregnancy test, if applicable	8.3.6	X	X[4]			X			X	X	
12-lead ECG[5]	8.3.7 Table 4	X	X (pre-dose, EOI, and 4 hr post-dose)	X (post-dose)	X	X (pre-dose, EOI, and 4 hr post-dose)	X	X (post-dose)	X[11]	X	
Premedication	6.7.1		D-1 to D2			D-1 to D2			D-1 to D2 for cycles containing loncastuximab tesirine		
Loncastuximab tesirine administration	6.3.1		X			X			D8 of Cycles 5 and 6 for patients who are PR or SD at Week 15 evaluation		
Durvalumab administration	6.3.2			X				X	X[8]		
Loncastuximab tesirine PK[5] sample	8.4.1 Table 5		X[5] (pre-dose, EOI, and 4 hr post-dose)	X	X	X (pre-dose, EOI, and 4 hr post-dose)	X	X	X[6] (pre-dose)	X	
Loncastuximab tesirine ADA[5] sample	8.4.1 Table 5		X[5] (pre-dose)		X	X (pre-dose)			X[6] (pre-dose)	X[7]	

	Protocol Section	Screening	Treatment Period							EOT	Follow-up Period (up to 2 years from EOT)
			Cycle 1 (3 week cycle)			Cycle 2 (6 week cycle)[9]			Cycle 3 and beyond (4 week cycles)		Every 12 weeks
Day (D)		**-28 to –1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Durvalumab PK sample	8.4.1							X[10]			
Concomitant medications	6.7.6	From ICF signature date or D-14, whichever is earlier, until 30 days after last dose of study drug(s)									
Adverse events	8.2	AE/SAEs from ICF signature date within 30 days after last dose of study drug(s); thereafter, related SAEs only									
1st New anti-cancer treatment										X	X
Survival										X	X

Abbreviations: ADA: anti-drug antibody; AE: adverse events; BP: blood pressure; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOT: end of treatment; HR: heart rate; ICF: informed consent form; PK: pharmacokinetics; RR: respiratory rate; SAE: serious AE; Temp: temperature; wks: weeks

Visit Scheduling Windows:

- Treatment Period: Visit day ± 2 days (excluding C1D1 which is the reference day).
- EOT: As soon as possible after decision to discontinue the study drug(s) but preferably within 30 days after last dose of study drug(s) unless a new anticancer treatment is planned to be administered before the 30 days, in which case EOT should be conducted before initiation of the new anticancer treatment.
- Follow-up Period: Visit day ± 14 days.

[1] Tumor biopsy should be obtained prior to study drug administration.
[2] Screening imaging (PET-CT) must be performed within 4 weeks prior to C1D1 and the same assessment method should be used throughout the study. Week 6 imaging should be performed prior to C3D1 and Week 15 imaging should be performed prior to C5D1. All other imaging for disease assessment for patients on study drug(s) should be performed within ± 2 weeks of the scheduled timepoint. Disease assessments should be performed at the timepoints specified even if study drug dosing is delayed. If a scan has been performed within 8 weeks of EOT, it does not need to be repeated at EOT.
[3] Disease assessments to be performed in patients having discontinued study drug(s) for reasons other than disease progression.
[4] Not needed if screening assessment was performed within 3 days prior to C1D1.
[5] On days when loncastuximab tesirine is administered, ECG, PK, and ADA timepoints are in relation to loncastuximab tesirine dose.
[6] Cycle 3, C5, C6, C7; see Table 5.
[7] Patients who test positive for loncastuximab tesirine ADAs may be requested to supply additional ADA samples as specified in the protocol, Section 8.4.2.
[8] Administration of durvalumab, C3D1 will be 4 weeks after C2D15.
[9] Cycle 2 will be 6 weeks long because durvalumab administration needs to be 4 weeks apart. C3D1 will be 4 weeks after C2D15.
[10] The durvalumab PK sample should be taken before durvalumab dose administration.
[11]Cycle 3.

1 Introduction and Background

1.1 Non-Hodgkin Lymphoma and CD-19

Non-Hodgkin lymphoma (NHL) represents a biologically and clinically diverse group of hematologic malignancies arising from precursor and mature B, T, and natural killer cells. It is the 7th most common type of cancer in the US and will account for an estimated 4.3% (n=72,240) of new cancer cases in 2017 (Siegel et al., 2017). In the United States, tumors of B-cell origin make up 85% to 90% of non-Hodgkin lymphoma.

Human CD19 antigen is a 95 kDa transmembrane glycoprotein belonging to the immunoglobulin superfamily. In normal human tissue, expression of CD19 continues through pre-B and mature B-cell differentiation until it is finally down-regulated during terminal differentiation into plasma cells (Scheuermann and Racila, 1995); however, expression of CD19 is maintained in hematologic B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL).

1.1.1 Diffuse Large B-cell Lymphoma

DLBCL accounts for an estimated 32.5% of NHL (Al-Hamadani et al., 2015). Standard first-line therapy uses immuno-chemotherapy such as R-CHOP. The response rate to front-line R-CHOP is > 80% but approximately 30% to 50% of patients with DLBCL are not cured, and most patients who fail a rituximab-containing chemotherapy regimen (e.g., R-CHOP) will die from their disease. Salvage therapy, including high-dose chemotherapy and autologous stem cell transplant (HD-ASCT), can be effective treatment for DLBCL patients with chemotherapy-sensitive relapse. However, over half of the patients treated in this fashion will not have long term disease control (Gisselbrecht et al., 2010). The prognosis of patients whose disease is refractory to initial chemotherapy and are therefore not eligible for HD-ASCT, or who relapse early after HD-ASCT, is extremely poor. These patients have a poor response to salvage therapy, with an overall response rate (ORR) of 26% (complete response [CR] rate 7%) and a median survival of approximately 6 months (Crump et al., 2017). The management of patients with DLBCL who are ineligible for HD-ASCT or who relapse after HD-ASCT is difficult. Additional immuno-chemotherapy following a second HD-ASCT or allogeneic stem cell transplant (AlloSCT) produces responses in only a small proportion of patients with substantial toxicity.

Recently, autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy (axicabtagene ciloleucel [Yescarta®] and tisagenlecleucel [Kymriah®]) has been shown to produce responses in ~50-70% of patients with relapsed or refractory DLBCL, with ~30-50% achieving CR. Durable responses have been achieved in patients who achieve a CR, but the duration of response (DOR) in patients with a partial response (PR) is short (2.1 months for axicabtagene ciloleucel). Moreover, there is significant toxicity, particularly cytokine release syndrome and neurologic events, including encephalopathy. It is only available at specialized centers and requires substantial lead-time for preparation, with approximately 10% of patients being unable to receive the planned therapy.

The poor prognosis for relapsed patients, especially those with chemotherapy-refractory disease with a short interval between remission and relapse or those who relapse after high-dose therapy and stem cell transplant (SCT), highlights the unmet medical need for more effective salvage treatments for patients with relapsed or refractory DLBCL (Coiffier and Sarkozy, 2016; Epperla and Hamadani, 2017).

1.1.2 Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a rare and aggressive form of non-Hodgkin lymphoma that predominantly affects older individuals. Standard first-line therapy uses immuno-chemotherapy. Patients who are eligible for consolidation with HD-ASCT are typically treated with cytarabine-based regimens. Patients who are not eligible for treatment with HD-ASCT receive regimens such as R-CHOP or R-bendamustine. Most patients (80-90%) respond to front-line therapy, but many will relapse. There are a number of agents available for second-line therapy, including bortezomib, lenalidomide, and ibrutinib. However, the response rates are low for bortezomib and lenalidomide at 33% and 28%, respectively. The response to ibrutinib is higher at 65%, but only 17% of these are CR. Thus, there remains unmet medical need for additional salvage treatments for patients with relapsed or refractory MCL (Campo and Rule, 2015).

1.1.3 Follicular Lymphoma

Follicular lymphoma (FL) is the most common type of indolent NHL, accounting for approximately 22% of all patients with NHL. Standard first-line therapy uses immuno-chemotherapy. Although current front-line regimens for Stages III and IV such as R-CHOP or R-bendamustine are associated with high response rates, most patients still relapse. There are a number of agents available for second-line therapy, including cytarabine-containing regimens and idelalisib (Zydelig®). It has been reported idelalisib is effective in patients with high-risk FL and early relapse after initial immune-chemotherapy, with 56.8% ORR, 13.5% CR rate, and 11.8 months duration of response (DOR) (Gopal et al., 2017). However, FL is characterized by successive lines of therapy resulting in progressively shorter periods of disease-free survival followed ultimately by the development of either chemo-refractoriness, large cell transformation, or death from treatment-related toxicities (Cheah and Fowler, 2018). Thus, there remains unmet medical need for novel drugs for patients with relapsed or refractory FL.

1.2 Loncastuximab Tesirine and Durvalumab

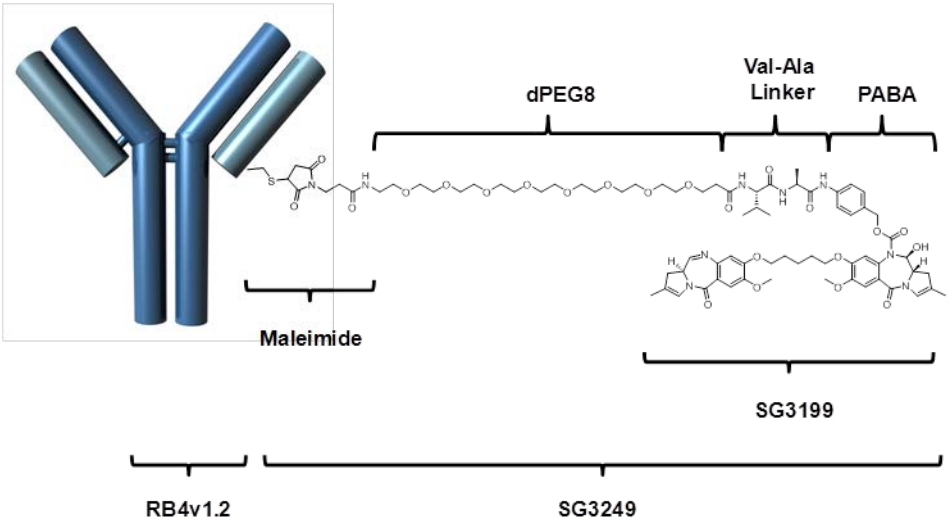
1.2.1 Loncastuximab Tesirine Description

Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate (ADC), composed of a humanized monoclonal antibody (RB4v1.2) directed against human cluster of differentiation 19 (CD19) conjugated through a cathepsin-cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin. The toxin SG3199 attached to the linker is designated as SG3249.

It is anticipated to become a component of combination therapies that increase the response rate and durability of treatment.

The schematic representation of loncastuximab tesirine is presented in Figure 1.

Figure 1 Schematic Representation and Chemical Structure of Loncastuximab Tesirine



Abbreviations: Ala, alanine; PABA, para-aminobenzoic acid; PEG, polyethylene glycol; RB4v1.2, humanized anti-CD19 monoclonal antibody; Val, valine.

Loncastuximab tesirine binds with picomolar affinity to human CD19. After binding and internalization, loncastuximab tesirine traffics to the lysosomes, where the protease-sensitive linker is cleaved and unconjugated PBD dimers (SG3199) are released inside the target cell. The released PBD dimers bind in the minor groove of deoxyribonucleic acid (DNA) and form potent cytotoxic DNA interstrand cross-links. The cross-links result in a stalled DNA replication fork, blocking cell division and causing cell death (Hartley, 2011). The cross-links formed by PBD dimers are relatively non-distorting to the DNA structure, making them hidden to repair mechanisms (Adair et al., 2012; Beck et al., 2017).

1.2.2 Safety and Efficacy of Loncastuximab Tesirine

ADCT-402-101 (NCT02669017) is a first-in-human Phase 1 dose escalation study of loncastuximab tesirine in relapsed or refractory B-cell NHL patients, who have failed or are intolerant to established therapies, or have no other treatment options available. The study design involves a dose escalation phase (Part 1) followed by a dose expansion phase (Part 2). The primary objectives for Part 1 were to evaluate the safety and tolerability of loncastuximab tesirine and to determine the maximum tolerated dose (MTD) and/or the recommended dose(s) to use in Part 2. The primary objective for Part 2 was to evaluate the safety and tolerability of the dose(s) determined in Part 1. The secondary objectives include evaluating the clinical activity of loncastuximab tesirine as measured by ORR, DOR, progression--free survival (PFS), and overall survival (OS).

As of data cut-off date of 03 December 2017, a total of 144 patients with relapsed or refractory B-cell NHL received at least one infusion of loncastuximab tesirine. The median age was 63.5 years (range: 23-86). The median number of previous chemotherapy regimens was 3 (range: 1-10) with 24.3% of patients having prior stem cell transplant.

Treatment-emergent adverse events (TEAEs) were reported in 137 (95.1%) out of 144 patients treated with loncastuximab tesirine. The most common TEAEs (observed in at least in 15% of patients), regardless of relationship to study treatment, were fatigue (42.4%); nausea (27.1%); gamma-glutamyltransferase (GGT) increased (26.4%); anemia (25.7%); edema peripheral (25.0%); dyspnea (18.8%); neutrophil count decreased, platelet count decreased, and thrombocytopenia (18.1% each); rash (17.4%); abdominal pain (16.0%); neutropenia (16.0%); and constipation (15.3%). Grade ≥3 TEAEs were reported in 92 (63.9%) patients. The most common Grade ≥3 TEAEs (observed in at least in 5% of patients) were neutrophil count decreased (16.0%); GGT increased (14.6%); anemia (12.5%); platelet count decreased (11.8%); neutropenia (11.1); and thrombocytopenia (8.3%).

The following events were considered non-serious adverse drug reactions (ADRs): GGT increased, edema (includes peripheral and facial), neutrophil count decreased, platelet count decreased, thrombocytopenia, neutropenia, and skin-related events (such as rash, maculopapular rash, and erythema).

TEAEs in 16 (11.1%) patients led to treatment discontinuation.

Dose-limiting toxicity (DLT) was reported in 3 patients (2 thrombocytopenia and 1 febrile neutropenia).

Serious adverse events (SAEs) were reported in 54 (37.5%) out of 144 patients. Of these, 24 patients experienced an SAE(s) considered at least possibly related to study drug. Six of the possibly related events were observed in multiple patients (febrile neutropenia in 5 patients, pyrexia in 3 patients, dyspnea in 2 patients, lung infection in 2 patients, pleural effusion in 2 patients, and sepsis in 2 patients). Preliminary data indicate an acceptable safety profile. Febrile neutropenia and pleural effusion have been classified as expected serious ADRs.

Out of 126 evaluable patients, 33 (26.2%) achieved CR and 25 (19.8%) achieved partial response (PR), for an ORR of 58/126 (46.0%).

Out of 92 evaluable patients with DLBCL, 22 (23.9%) achieved CR and 16 (17.4%) achieved PR, for an ORR of 38/92 (41.3%).

The MTD was not formally established, but the recommended maximum Phase 2 dose was determined to be 150 µg/kg based on tolerability and antitumor efficacy.

Additional details may be found in the current loncastuximab tesirine Investigator's Brochure.

1.2.3 Durvalumab Description

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of programmed death-ligand 1 (PD-L1) [but not programmed cell death ligand-2] with PD-1 on T cells and CD80 (B7.1) on other immune cells. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon gamma (IFN-γ) (Stewart et al., 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al., 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given either as monotherapy or in combination with other anticancer agents to more than 6000 patients as part of ongoing studies.

Checkpoint activation is an immune-evasion strategy that is operative in various tumors, both solid and hematological. There is pre-clinical evidence suggesting that the combination of an antibody-drug conjugate (ADC) and a checkpoint inhibitor (such as a PD-L1 blocker) may be more potent than either of the respective monotherapies (Müller et al., 2015). Early results from clinical trials combining ADCs and checkpoint inhibitors show potential increased effectiveness of the combination (Diefenbach et al., 2015; Diefenbach et al., 2016).

1.2.4 Safety and Efficacy of Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ interstitial lung disease (ILD), endocrinopathies (i.e., events of hypophysitis, adrenal insufficiency, hyperthyroidism and hypothyroidism, and Type 1 diabetes mellitus), hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/dermatitis, myocarditis, myositis/polymyositis, and other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.

In monotherapy clinical studies, adverse events (AEs) reported very commonly include events such as fatigue, diarrhea, nausea and vomiting, decreased appetite, and muscle and joint pain. A total of 5% to 10% of patients discontinued the drug due to an AE. The majority of treatment-related AEs were manageable, with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 13.3, Appendix 3).

Additional details may be found in the current version of the durvalumab IB.

2 Study Rationale

While both loncastuximab tesirine and durvalumab have shown antitumor activity as single agents, a substantial proportion of patients will not have a complete response to either agent, and many patients will progress at some point. Combining two agents with different mechanisms of action has the potential to increase activity compared to either agent alone. Thus, combining an ADC such as loncastuximab tesirine with a PD-L1 inhibitor, such as durvalumab, represents a rational approach for study in the clinic.

2.1 Rationale for Study Design

As loncastuximab tesirine and durvalumab represent a novel combination, the study will have dose finding using a standard 3+3 dose escalation design, followed by a dose expansion. As toxicity seemed similar across histologies in the Phase 1 study of loncastuximab tesirine, the dose escalation will enroll all histologies. To ensure adequate number of patients for the less common histologies of MCL and FL, the dose expansion will have individual cohorts for each histology.

2.2 Rationale for Dose Selection

Durvalumab will be administered as a fixed dose based on a population pharmacokinetic (PK) analysis that indicated only a minor impact of body weight on the PK of durvalumab. The dose of 1500 mg corresponds to a dose of 20 mg/kg, which was the highest dose tested in clinical trials and was well tolerated. As this is a novel combination, loncastuximab tesirine will be administered starting with a dose of 90 µg/kg, which is 60% of the recommended Phase 2 dose. In treatment cycles where both drugs are given, they will be administered sequentially 1 week apart, with loncastuximab tesirine being given first in the initial 2 treatment cycles to allow for potential immunogenic cell death, which could enhance the activity of durvalumab.

3 Study Objectives and Endpoints

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of loncastuximab tesirine in combination with durvalumab, and to identify the recommended dose and schedule for future studies	• Frequency and severity of adverse events (AEs and serious adverse events (SAEs • Incidence of dose-limiting toxicities (DLTs) in the 21 days after the first durvalumab dose (dose escalation only) • Frequency of dose interruptions and dose reductions • Changes from baseline of safety laboratory values, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs)
Secondary	
• To evaluate the antitumor effect of the combination of loncastuximab tesirine with durvalumab • To characterize the pharmacokinetic (PK profile of loncastuximab tesirine when given in combination with durvalumab • To evaluate the immunogenicity of loncastuximab tesirine when given in combination with durvalumab	• Overall response rate (ORR according to the 2014 Lugano classification as determined by the Investigator. ORR is the proportion of patients with a best overall response (BOR) of complete response (CR or partial response (PR • Duration of response (DOR defined as the time from the documentation of first tumor response to disease progression or death • CR rate defined as the percentage of patients with a BOR of CR • Relapse-free survival (RFS) defined as the time from the documentation of CR to disease progression or death • Progression free survival (PFS) defined as the time between start of treatment and the first documentation of progression, or death • Overall survival (OS) defined as the time between the start of treatment and death from any cause • Concentrations and PK parameters of loncastuximab tesirine (total antibody, PBD-conjugated antibody, and unconjugated cytotoxin SG3199) • Anti-drug antibody (ADA) titers and, if applicable, neutralizing activity to loncastuximab tesirine
[redacted]	
[redacted]	[redacted]

4 Study Design

4.1 Overview

This is a Phase 1b, open-label, single-arm combination study with a dose escalation phase (Part 1) followed by a dose expansion phase (Part 2). The study will enroll approximately 75 patients.

A standard 3+3 dose escalation design will be used for Part 1. The DLT evaluation period will be 21 days after the first durvalumab dose.

Part 2 will consist of up to 3 expansion cohorts, one for DLBCL, one for MCL, and one for FL. Each cohort will be approximately 20 patients treated at the dose determined in Part 1.

The study will include a Screening Period (of up to 28 days), a Treatment Period (cycles of 3, 6, and 4 weeks), and a Follow-up Period (approximately every 12 week visits for up to 2 years after treatment discontinuation).

4.2 Screening Period

Informed consent must be obtained for each patient and documented with a signed informed consent form (ICF) prior to any study procedures. Procedures that are performed as part of standard of care may be used to satisfy screening requirements if they are performed in the screening window.

The screening period is from 28 days to 1 day prior to the start of the study drug. The screening assessments should be performed within this period in order to assess the eligibility of the patient against the inclusion and exclusion criteria (Sections 5.1 and 5.2, respectively).

See Section 5.3 for the information to be collected on screening failures.

4.3 Treatment Period

The treatment period starts on the date when a patient receives the first dose of study drug and continues until the End of Treatment (EOT) visit.

The treatment will start with Cycle 1, which will be 3 weeks long (i.e., 21 days), Cycle 2 will be 6 weeks long because durvalumab administration needs to be 4 weeks apart, and all other subsequent cycles will be 4 weeks long. Loncastuximab tesirine will be administered as an intravenous (IV) infusion over 30 minutes on Day 1 of Cycles 1 and 2. All patients will receive loncastuximab tesirine every 3 weeks (Q3W) for 2 cycles. Patients who have a response of PR or stable disease (SD) at the Week 15 assessment may receive an additional 2 doses of loncastuximab tesirine given on day 8 of Cycles 5 and 6.

Durvalumab will be administered as an IV infusion over 60 minutes on Day 8 of Cycle 1 and Day 15 of Cycle 2, then on Day 1 of subsequent cycles.

Patients may continue treatment for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria (Section 7), whichever occurs first.

4.4 End of Treatment

The EOT visit should be performed as soon as possible after the decision to discontinue the study drug, preferably within 30 days after last dose of study drug and before initiation of any new anticancer treatment.

When EOT coincides with a scheduled visit, the scheduled visit will become EOT.

4.5 Follow-up Period

All patients, regardless of disease status, will be followed every 12 weeks for up to 2 years from EOT, or until withdrawal of consent, loss to follow-up, or death, whichever occurs first.

When disease assessments are not planned for a follow-up visit, the visit can be done by phone.

4.6 End of Study

The end of study for each patient will be the date of last visit/contact or date of death, whichever occurs last, and the end of study for the study as a whole will be the last visit or last scheduled procedure for the last patient, unless the study is terminated earlier by the Sponsor.

5 Patient Population

Patients must meet all inclusion criteria and none of the exclusion criteria to be eligible for the study. All criteria have to be assessed at Screening, unless otherwise specified (e.g., criterion to be confirmed within 28 days to 1 day prior to the start of study drug on Cycle 1 Day 1 [C1D1]).

5.1 Inclusion Criteria

1. Male or female patient aged 18 years or older
2. Pathologic diagnosis of DLBCL, MCL, or FL
3. Patients must have relapsed or refractory disease and have failed or been intolerant to standard therapy
4. Patients who have received previous CD19-directed therapy must have a biopsy that shows CD19 expression after completion of the CD19-directed therapy
5. Measurable disease as defined by the 2014 Lugano Classification
6. Patients must be willing to undergo tumor biopsy
7. ECOG performance status 0-1
8. Screening laboratory values within the following parameters:
   a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu L$ (off growth factors at least 72 hours)
   b. Platelet count $\geq 75 \times 10^3/\mu L$ without transfusion in the past 7 days
   c. Hemoglobin ≥9.0 g/dL (5.59 mmol/L), transfusion allowed
   d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and GGT ≤2.5 × the upper limit of normal (ULN)
   e. Total bilirubin ≤1.5 × ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 × ULN)
   f. Blood creatinine ≤1.5 × ULN or calculated creatinine clearance ≥60 mL/min by the Cockcroft-Gault equation

   Note: A laboratory assessment may be repeated a maximum of two times during the Screening period to confirm eligibility.
9. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test within 3 days prior to start of study drug on C1D1 for women of childbearing potential
10. Women of childbearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of study therapy. Men with female partners who are of childbearing potential must agree that they will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of study therapy.

* Women of childbearing potential are defined as sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least 1 year.

** Highly effective forms of birth control are methods that achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective forms of birth control include: hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient.

Note: The double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only are not acceptable as highly effective methods of contraception.

5.2 Exclusion Criteria

1. Known history of hypersensitivity to or positive serum human ADA to a CD19 antibody
2. Previous therapy with any checkpoint inhibitor
3. Autologous stem cell transplant within 100 days prior to start of study drug (C1D1)
4. History of allogenic stem cell transplant
5. History of solid organ transplant
6. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:
    a. Patients with vitiligo or alopecia
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    c. Any chronic skin condition that does not require systemic therapy
    d. Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician
    e. Patients with celiac disease controlled by diet alone
7. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice)
8. Known seropositive and requiring anti-viral therapy for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV)

9. History of Stevens-Johnson syndrome or toxic epidermal necrolysis
10. Lymphoma with active central nervous system involvement at the time of screening, including leptomeningeal disease
11. Clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath)
12. Breastfeeding or pregnant
13. Significant medical comorbidities, including but not limited to, uncontrolled hypertension (blood pressure [BP] ≥160/100 mmHg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 6 months prior to screening, uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, or severe chronic pulmonary disease
14. Radiotherapy, chemotherapy, or other anti-neoplastic therapy within 14 days prior to start of study drug (C1D1), except shorter if approved by the Sponsor
15. Major surgery within 28 days prior to start of study drug (C1D1), except shorter if approved by the Sponsor. Note: Local surgery of isolated lesions for palliative intent is acceptable
16. Use of any other experimental medication within 14 days prior to start of study drug (C1D1)
17. Planned live vaccine administration after starting study drug (C1D1)
18. Failure to recover to Grade ≤1 (Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) from acute non-hematologic toxicity (Grade ≤2 neuropathy or alopecia) due to previous therapy prior to screening
19. Congenital long QT syndrome or a corrected QTcF interval of >470 ms at screening (unless secondary to pacemaker or bundle branch block)
20. History of another primary malignancy except for:
    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of investigational product and of low potential risk for recurrence
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c. Adequately treated carcinoma in situ without evidence of disease
21. History of active primary immunodeficiency
22. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgement, make the patient inappropriate for study participation or put the patient at risk.

5.3 Screen Failures

Patients who signed the ICF but were found not eligible for the study prior to receiving study drugs are defined as screening failures.

For these patients, only limited information will be collected in the electronic case report form (eCRF):

- Informed consent
- Demographics
- Inclusion/exclusion criteria
- SAE and/or death occurring during the screening period

6 Study Treatment

6.1 Study Drugs

6.1.1 Loncastuximab Tesirine

Loncastuximab tesirine will be provided as a frozen liquid formulation in 10 mL glass vials designed to deliver 3.2 mL of loncastuximab tesirine at a concentration of 5 mg/mL (16 mg loncastuximab tesirine per vial) and stored at -65°C or below. It is a sterile, frozen liquid formulated in 30 mM histidine, 200 mM sorbitol, and 0.02% polysorbate 20, at pH 6.0. Prior to use, the frozen formulation is thawed at ambient temperature, gently swirled to ensure homogeneity, and visually inspected.

6.1.2 Durvalumab

Durvalumab will be supplied as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. Durvalumab vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

6.2 Management of Clinical Supplies

Detailed instructions regarding shipment of study drugs, handling, storage, and preparation are included in the pharmacy manual.

6.2.1 Packaging and Storage

The study drugs will be supplied by the Sponsor through the designated distribution center.

Once the package arrives at the study site, the receiving site pharmacy will complete the procedures listed in the pharmacy manual to acknowledge receipt.

All study drugs must be stored in a secure area.

- Loncastuximab tesirine liquid formulation: loncastuximab tesirine should be protected from light and stored frozen (-65°C or below). Loncastuximab tesirine should be thawed under ambient conditions.

- Unopened vials of durvalumab must be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

6.2.2 Preparation and Administration

Loncastuximab tesirine solution at the concentration of 5 mg/mL will be the basis for the preparation of the infusion solution. The amount of loncastuximab tesirine to be administered will depend on the dose level and the weight of the patient. Loncastuximab tesirine will be administered as a 30 minute IV infusion. Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.

Durvalumab will be given as a fixed dose of 1500 mg administered as a 60 minute IV infusion. Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.

6.2.3 Accountability

The Investigator must maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records must be kept regarding when and how much study drugs are dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. All study drugs must be reconciled and retained or destroyed according to applicable regulations.

6.3 Dosing of Study Drugs

6.3.1 Loncastuximab Tesirine Dosing

Administration of loncastuximab tesirine will be performed by the Investigator or a qualified designee.

During Part 1, loncastuximab tesirine will be administered on Day 1 of Cycle 1 and Cycle 2 per the dose escalation plan as shown below.

Loncastuximab tesirine will be given initially for 2 doses, 3 weeks apart.

Loncastuximab Tesirine Dose Escalation

Dose Level	Loncastuximab tesirine	Durvalumab
1	90 μg/kg IV on Day 1 Q3W × 2	1500 mg IV Q4W
2	120 μg/kg IV on Day 1 Q3W × 2	1500 mg IV Q4W
3	150 μg/kg IV on Day 1 Q3W × 2	1500 mg IV Q4W

Patients who have a response of PR or SD at the 15 week assessment may receive two additional doses of loncastuximab tesirine given 4 weeks apart.

Patients with a body mass index (BMI) ≥35 kg/m^2 will have their loncastuximab tesirine dose calculated based on an adjusted body weight as follows:

- Adjusted body weight (ABW) in kg = 35 kg/m^2 * (height in meters)^2
- Dose to administer (mg) = dosage (µg/kg) * ABW/1000

During Part 2, patients will receive loncastuximab tesirine on Day 1 of Cycle 1 and Cycle 2 at the recommended dose determined in Part 1. Patients who have a response of PR or SD at the 15 week assessment may receive 2 additional doses of loncastuximab tesirine given 4 weeks apart.

Refer to Section 6.7 for premedication and supportive care.

6.3.2 Durvalumab Dosing

Administration of durvalumab will be performed by the Investigator or a qualified designee.

Durvalumab will be administered at a fixed dose of 1500 mg every 4 weeks. Durvalumab will be administered on Day 8 of Cycle 1, Day 15 of Cycle 2, and Day 1 of subsequent cycles.

6.4 Dose Escalation

6.4.1 Dose Escalation Design

The dose escalation of loncastuximab tesirine in Part 1 will follow a standard 3+3 design using the dose levels defined in Section 6.3.1. Cohorts of 3 patients will be treated, starting at the initial dose level. If 0 of 3 patients in the first cohort at any dose level experience a DLT, then the following cohort will be treated at the next higher dose level. If 2 of 3 patients experience a DLT, then the preceding dose level will be determined as the MTD. If 1 of 3 patients experience a DLT, then 3 additional patients will be treated at that dose level. If 0 of 3 additional patients experience a DLT, then the following cohort will be treated at the next higher dose level. If 1 or more of 3 additional patients experience a DLT, then the preceding dose level will be determined as the MTD.

Patients in Part 1 without a DLT who discontinue from the study prior to completion of the DLT period will be replaced.

6.4.2 Dose Limiting Toxicity Period

For patients in Part 1, the DLT period will be the 21 days after the first durvalumab dose. Any treatment-related toxicities that first occurred during the DLT period must be followed for resolution to determine if they qualify as a DLT as specified in the DLT criteria below.

6.4.3 Dose Limiting Toxicity Definition

A DLT defined as any of the following events, which occur during the 21-day DLT evaluation period of Part 1, except those that are clearly due to underlying disease or extraneous causes:

A **hematologic** DLT is defined as:

- Grade 4 anemia
- Grade 3 anemia requiring transfusion
- Grade 4 neutropenia lasting > 7 days
- Febrile neutropenia
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia which results in clinically significant bleeding or requires a transfusion

A **non-hematologic** DLT is defined as:

- Hy's law case - AST and/or ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN, and without initial findings of cholestasis (serum alkaline phosphatase [ALP] activity < 2 × ULN) and no other reason that could explain the combination of increased transaminases and serum total bilirubin
- Any other non-hematologic toxicity ≥ Grade 3 with the exception of the following:
  - Grade 3 fatigue for ≤ 7 days.
  - Grade 3 nausea, vomiting, or diarrhea in the absence of premedication that responds to therapy and improves by at least 1 grade within 3 days or to ≤ Grade 1 within 7 days.
  - Grade 3 elevations of ALP and GGT elevations, unless considered clinically relevant by the Investigator.
  - Grade 3 elevation of serum lipase or serum amylase for ≤ 7 days if without clinical signs or symptoms of pancreatitis.
  - Grade 3 electrolyte abnormalities that normalize within 48 hours (with or without medical intervention) and that do not manifest themselves clinically; in such instance, a follow-up sample MUST be taken within 48 hours to check whether such normalization has occurred.

- In addition, the following will be considered DLTs:
    - Grade 2 noninfectious pneumonitis that does not resolve to ≤Grade 1 within 3 days of the initiation of maximal supportive care
    - Any grade of immune-mediated rash with bullous formation
    - Grade 2 or 3 immune-mediated peripheral neuromotor syndrome (such as Guillain-Barre and myasthenia gravis) that does not resolve to Grade ≤1 within 30 days or that exhibits signs of respiratory insufficiency or autonomic instability
    - Grade 2 immune-mediated myocarditis that does not resolve to Grade ≤1 within 3 days of initiating optimal medical management, including systemic corticosteroids
    - Grade 2 or 3 immune-mediated myositis/polymyositis that does not resolve to Grade ≤1 within 30 days of initiating optimal medical management, including systemic corticosteroids, or that exhibits signs of respiratory insufficiency regardless of optimal medical management
    - Immune-mediated increase in creatinine >3 × ULN, or >3 × baseline for patients with a baseline creatinine elevated above ULN

Patients who experience a DLT that resolves or stabilizes with appropriate medical management may continue treatment at the discretion of the Investigator in consultation with the Sponsor.

6.4.4 Dose Escalation Steering Committee

A Dose Escalation Steering Committee (DESC) will oversee dose escalation and general safety of the study.

Membership of the DESC will include:

- Medical and/or pharmacovigilance representative(s) from the Sponsor and/or designee
- Investigator(s) from each participating site

The DESC will be responsible for:

- Determining dose levels to be administered and the MTD based on assessment of safety findings and DLTs.
- Monitor the safety of the study and review its progress at monthly intervals or more frequently as required.

Decisions made at DESC meetings will be documented in written minutes, which will be distributed to DESC members.

6.5 Dose Delays and Modifications

6.5.1 Loncastuximab Tesirine

If a patient experiences any Grade ≥3 (≥2 for edema, effusion, or increased AST/ALT/GGT) toxicity, loncastuximab tesirine must be held until the toxicity resolves to Grade 1 or less (Grade 1 or baseline for peripheral neuropathy). If loncastuximab tesirine dosing is delayed by more than 3 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, then subsequent doses of loncastuximab tesirine will be reduced by 50%.

In addition, the Investigator may reduce the dose of loncastuximab tesirine by 50% for any Grade ≥3 (≥2 for edema, effusion, or increased AST/ALT/GGT) toxicity that is possibly related to loncastuximab tesirine but does not result in dosing delay of more than 3 weeks if they feel it is in the best interest of the patients.

6.5.2 Durvalumab

If a patient experiences any Grade ≥3 toxicity, durvalumab must be held until the toxicity resolves to Grade 1 or less (Grade 1 or baseline for peripheral neuropathy).

In addition, durvalumab must be held for the following Grade ≥2 specific immune-mediated toxicities:

- Pneumonitis/ILD
- Diarrhea/Colitis
- Hepatitis (elevated liver function tests)
- Nephritis or renal dysfunction
- Persistent rash (>1-2 weeks)
- Endocrinopathy (except isolated hypothyroidism or Type 1 diabetes mellitus)
- Neurotoxicity
- Peripheral neuromotor syndromes
- Myocarditis
- Myositis/polymyositis

See Section 13.3, Appendix 3 for guidelines regarding management and resumption of durvalumab therapy after specific immune-mediated toxicities.

For all other toxicities, durvalumab must be held until the toxicity resolves to Grade 1 or less (Grade 1 or baseline for peripheral neuropathy).

Durvalumab will be given at full dose when resumed after being held for toxicity, i.e., there will be no dose reduction.

6.6 Overdose Management

An overdose is any dose of study drug(s) given to a patient that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the Sponsor. There are no data available to determine what the effects of overdose of loncastuximab tesirine are and whether they can be reversed. There is no specific experience in the management of durvalumab overdose in patients. Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

6.7 Premedication and Supportive Care

6.7.1 Premedication

Unless contraindicated, administer dexamethasone 4 mg PO or IV twice daily:

- the day before each loncastuximab tesirine administration (if possible),
- the day of loncastuximab tesirine administration (first dose at least 2 hours prior to administration when not given the day before; otherwise any time prior to administration), and
- the day after loncastuximab tesirine administration.

Patients who experience an infusion-related hypersensitivity reaction will receive the alternative premedication regimen specified in Section 6.7.3.

6.7.2 Treatment of Edema and Pleural Effusion

Peripheral edema and serosal effusions (pleural and pericardial effusions, ascites) have been seen in patients receiving loncastuximab tesirine. Patients should be advised to monitor their weight on a daily basis (preferably each morning around the same time) and notify the study site of weight gain greater than 1 kg from baseline.

Patients with weight gain greater than 1 kg from baseline, new or worsening edema, and/or new or worsening pleural effusion, pericardial effusion, or ascites, should be treated with spironolactone at standard doses. The dose of spironolactone may be titrated as clinically indicated. Additional diuretic support may be added if there is further increase in weight, edema, or effusion.

6.7.3 Treatment and Prophylaxis of Infusion-related Hypersensitivity Reactions

Medications for the treatment of severe hypersensitivity reactions, including anaphylaxis, should be available for immediate use and may be administered according to institutional standard of care.

Any patient who experiences an infusion-related hypersensitivity reaction should receive prophylactic treatment in subsequent cycles according to the guidelines below or as per institutional standard of care:

- On Day 1 of each cycle, patients should receive dexamethasone 20 mg PO or IV 12 and 6 hours before the start of the loncastuximab tesirine infusion. When necessary, 12 and 6 hours before the first infusion may be defined as "immediately before sleeping" and "immediately after waking up."
- On Day 1 of each cycle, patients will be given diphenhydramine hydrochloride 50 mg IV 30 minutes before the start of the loncastuximab tesirine infusion.
- On Day 1 of each cycle, patients will be given ranitidine (or equivalent) 50 mg IV 30 minutes before the start of the loncastuximab tesirine infusion.
- For 2 days following administration of loncastuximab tesirine on Day 1, patients are to take dexamethasone 4 mg PO or IV twice daily (BID).

6.7.4 Skin Rash

Skin rash has been reported with loncastuximab tesirine, as well as with another investigational agent containing the same PBD warhead (Rudin et al., 2017). The rash has been reported in areas at risk for sun exposure; it is therefore recommended that precautions are taken to avoid prolonged exposure of skin to sunlight.

6.7.5 Other Supportive Care

- Although the study patient population has a low risk for development of tumor lysis syndrome (TLS) compared to patients with acute disease (Cairo et al., 2010), patients should be observed for development of TLS and treated according to site standard treatment protocols.
- As testing in animals showed testicular toxicity (atrophy with reduced spermatogenesis), male patients are advised to consider cryopreservation of sperm prior to treatment with loncastuximab tesirine, where applicable.

6.7.6 Concomitant Medications and Procedures

Medications (except for the study drugs) and procedures will be recorded in the eCRF starting from the ICF signature date or from 14 days prior to C1D1, whichever is earlier, and continuing until 30 days after last dose of study drug.

6.7.7 Permitted During Study

All medications or procedures for the clinical care of the patient, including management of AEs, are permitted during the study, except for those listed in Section 6.7.8.

Hematopoietic growth factors are permitted as per American Society of Clinical Oncology guidelines (Smith et al., 2006).

6.7.8 Prohibited During Study

- Other anticancer therapy with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer.
- Other investigational agents.
- Live vaccines including for 30 days after the last dose of durvalumab.
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection)
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    - Steroids as premedication for hypersensitivity reactions (e.g., computed tomography [CT] scan premedication)

7 Discontinuation

The reason for discontinuation and the date of discontinuation will be collected for all patients.

Note: Once discontinued from the study for any reason, patients are not permitted to be re-enrolled.

7.1 Discontinuation from Study Treatment

A patient may be discontinued from study treatment for any of the following reasons:

- Disease progression
- Unacceptable toxicity
- Patient decision
- Major protocol deviation
- The Investigator determines that it is in the best interest of the patient to discontinue the patient's participation in the study
- Discontinuation of the study by the Sponsor
- Pregnancy
- Death

IMPORTANT: Study treatment discontinuation is not to be automatically considered as withdrawal from the study. Patients discontinuing study treatment will be asked to perform an EOT visit (Section 4.4) and continue with the Follow-up period (Section 4.5) as per protocol.

The investigational site should make every effort to complete follow-up per protocol. If patients are unable to return to the site, patient status, including but not limited to survival status, may be obtained by site staff via phone, email, or mail.

7.2 Discontinuation from the Study

A patient may be discontinued from the study for any of the following reasons:

- Withdrawal of consent
- Investigator/Sponsor decision
- Death
- Loss to follow-up

If a patient withdraws consent, no additional data will be collected. The Sponsor may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

The study may be terminated at any time, for any reason, by the Sponsor. Patients still receiving study drug(s) should have an EOT visit as described in Section 4.4 and Schedule of Events (SoE) (Table 1).

7.3 Loss to Follow-up

Patients who fail to return for protocol follow-up are to be contacted by the investigative site. Following a minimum of two documented unsuccessful telephone calls, the investigative site should send a registered letter to the patient in a final attempt to ensure protocol compliance.

8 Study Assessments and Procedures

Informed consent, as documented by a signed and dated ICF, must be obtained prior to performing any study procedures. Results (e.g., from laboratory tests or radiographic evaluations, etc.) obtained prior to the date of informed consent but within the allowed timeframe for screening may be used for determination of patient eligibility only if obtained as part of standard care.

8.1 Efficacy Assessments

Disease assessments will occur as per SoE (Table 1) until progression. Disease assessments should take place at the timepoints specified even if dosing of study drug(s) is delayed. Additional disease assessments may be obtained, if clinically indicated.

Clinical examination for lymphoma will be performed at all disease assessment timepoints. Positron emission tomography-computed tomography (PET-CT) of the neck/chest/abdomen/ pelvis and other areas of known disease or newly suspected disease will be performed at baseline. Patients with PET-avid disease at baseline should have PET-CT for all subsequent disease assessments until they achieve CR. Patients who achieve CR may have CT with contrast for subsequent disease assessments. If disease is not PET-avid at baseline, CT with contrast or magnetic resonance imaging (MRI) may be used for all subsequent disease assessments.

Screening (Baseline) imaging must be performed within 4 weeks prior to C1D1.

During the treatment period, imaging will be performed 6 weeks and 15 weeks after C1D1, then every 8 weeks until EOT. Week 6 imaging should be performed prior to C3D1. Week 15 imaging should be performed prior to C5D1. All other imaging should be performed within ± 2 weeks of the scheduled time point.

During the follow-up period, patients who discontinued study drug(s) for reasons other than disease progression or initiation of other anti-cancer therapy, except stem cell transplant, will have imaging performed every 12 (± 2) weeks until 1 year from EOT, then every 6 months until disease progression, up to 2 years from EOT.

If a scan has been performed within 8 weeks of EOT, it does not need to be repeated at EOT.

In case of dose delays, disease assessment should be maintained at the frequencies defined above.

The patient's response to treatment will be determined according to the 2014 Lugano Classification Criteria (Section 13.2, Appendix 2) as CR, PR, SD, or progressive disease (PD). Images will be obtained according to local site imaging protocols

8.2 Adverse Events

8.2.1 Definition of Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment.

Test results collected during the study (e.g., laboratory values, physical examination, ECGs, etc.) or identified from review of other documents may constitute AEs if deemed clinically significant.

A SAE is defined as any AE that:

- results in death.
- is life threatening.
- requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization for elective procedures or for protocol compliance is not considered an SAE).
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- important medical events that do not meet the preceding criteria but based on appropriate medical judgement may jeopardize the patient or may require medical or surgical intervention to prevent any of the outcomes listed above.

8.2.2 Eliciting and Reporting Adverse Events/Serious Adverse Events

Patients will be instructed to contact the Investigator at any time after ICF signature if any symptoms develop. At each study visit, patients will be asked a non-leading question to elicit any medically related changes in their well-being. Patients may also report AEs voluntarily and they will be instructed to contact the Investigator between visits if any symptoms develop or worsen.

AEs will be reported starting when the patient provides written informed consent. Clinically significant medical conditions present at the time of ICF signature will be reported as medical history. Clinically significant medical conditions that start or worsen after ICF signature will be reported as AEs.

All AE/SAEs, regardless of relationship to study drug, will be reported from the time the patient signs the ICF until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs earlier; thereafter, only related SAEs will be reported.

Whenever possible, AEs should be reported as a diagnosis rather than individual signs and symptoms. If no diagnosis is available or has been identified, then the primary symptom is reported.

In general, the term 'disease progression' should not be used for reporting an AE/SAE. However, AEs/SAEs that are complications of disease progression should be reported.

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected will include event term, date of onset, assessment of severity (Section 8.2.3), seriousness (Section 8.2.1), relationship to study drug(s) (Section 8.2.4), action taken with study drug, date of resolution of the event or ongoing (when no resolution by the end of the reporting period), any required treatment or evaluations, and outcome.

New SAEs and any recurrent episodes, progression, or complications of the original SAE must be reported to the pharmacovigilance department of the Sponsor or delegate (e.g., contract research organization [CRO]) within 24 hours after the time site personnel first learn about the event. Reporting will occur through the electronic data capture (EDC) system.

8.2.3 Assessment of Severity

AEs will be graded according to CTCAE v4.0 (or more recent). For events not included in the CTCAE criteria, the severity of the AE is graded on a scale of 1 to 5 as shown in Table 3.

Table 3 Definition of Severity Grades for CTCAE

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

[a] ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AEs characterized as intermittent do not require documentation of onset and duration of each episode.

8.2.4 Assessment of Causality

The Investigator's assessment of an AE's relationship to study drug(s) is an important part of safety reporting. However, it is not a factor in determining whether or not an AE is reported. An AE will be assessed as related to study drug(s) if there is a reasonable possibility of causal relationship with the use of the study drug. For SAEs, whenever possible, the Investigator should provide a rationale for the causality assessment.

8.2.5 Regulatory Reporting

All SAEs considered at least possibly related to the study drug(s) will be reported as Suspected Unexpected Serious Adverse Reactions (SUSARs), unless they have been defined as expected in the Reference Safety Information section of the IB, and package insert for durvalumab. SUSARs will be reported to competent authorities and the Independent Ethics Committee (IEC) in accordance with current legislation.

8.2.6 Pregnancy

Any pregnancy in a participant or partner that occurs during the study must be reported using the Pregnancy Report Form. Pregnancy must be reported within 24 hours after the site personnel first learn of the pregnancy. The pregnancy itself is not considered an AE. However, the pregnancy must be followed to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient discontinued from the study. Abortions (elective or spontaneous) occurring from the time the patient signs the ICF until 90 days after the last dose of study drug(s) must be reported as an SAE.

Any SAE occurring in association with a pregnancy that is brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study drug(s) must be promptly reported in the same manner.

Once pregnancy is confirmed in a study participant, study drugs will be discontinued, see Section 8.3.6 for additional information.

8.3 Safety Assessments

Safety will be assessed based on the procedures in the subsection below. AE/SAE collection and reporting is described in Section 8.2.

Unless otherwise specified, all safety assessments on dosing days will be done prior to administration of study drug(s).

8.3.1 Physical Examination

Physical examination will be performed according to institutional standards and will include a whole body skin examination. Physical examinations will occur at the timepoints shown on Table 1.

8.3.2 ECOG Performance Status

ECOG performance status grades are presented in Section 13.1, Appendix 1 and will be captured as per SoE (Table 1).

8.3.3 Height and Weight

Height and weight will be measured as per SoE (Table 1).

Additional measurements should be performed if clinically indicated.

Patients should monitor their weight at home to mitigate the risks for edema/effusions. Refer to Section 6.7.2 for further details.

8.3.4 Vital Signs

Vital signs include the measurements of arterial blood pressure (systolic and diastolic), heart rate, respiratory rate, and body temperature and should be performed according to the institutional standards, see timepoints shown on Table 1. Vital signs should be measured before and after each loncastuximab tesirine infusion and each durvalumab infusion.

8.3.5 Laboratory Tests

Samples will be collected at the time points specified as per SoE (Table 1).

Hematology: white blood cells (WBCs) with 5-part differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, hemoglobin, and hematocrit.

Chemistry: ALT, AST, GGT, ALP, amylase, lipase, total bilirubin (conjugated and unconjugated bilirubin only when total is abnormal), sodium, potassium, chloride, phosphate/ phosphorus, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, creatinine, creatine phosphokinase, total protein, albumin, glucose and lactate dehydrogenase.

Coagulation: partial thromboplastin time and International Normalized Ratio.

Urinalysis: pH, specific gravity, protein, WBC, red blood cell (RBCs), ketones, glucose, and bilirubin.

Urinalysis may be performed by dipstick. Abnormal findings should be followed up with a microscopic evaluation and/or additional assessments as clinically indicated. A microscopic evaluation consists at a minimum of WBC and RBC quantitation per high power field, as well as semi-quantitative assessment of other cells and substances, if present, such as epithelial cells, bacteria, and crystals (“few,” “moderate,” “many”). Other evaluations depending on microscopic findings may be added.

Other Tests: TSH, (reflex free T3 or free T4). Hepatitis B, C, and HIV.

8.3.6 Pregnancy Test

A highly sensitive β-HCG test in urine or blood β-HCG test must be performed in women of childbearing potential (WOCBP) for eligibility (see Section 5.1) and throughout the study as per SoE.

The C1D1 pre-dose pregnancy test can be waived if the test for eligibility was done within 3 days of C1D1. After starting the study drug, all efforts should be made to keep the interval between 2 consecutive pregnancy tests no more than 6 weeks.

If a pregnancy test is positive, study drug must be held pending confirmation. If the pregnancy is confirmed, treatment must be discontinued permanently for the patient. Refer to Section 8.2.6 for the handling of the patient and reporting the event.

8.3.7 ECG

Three consecutive (also called triplicate) 12-lead ECGs will be performed at defined timepoints throughout the study as per SoE (Table 1). Refer to Table 4 for the detailed schedule of ECGs.

ECGs should be performed after the patient is resting for at least 5 minutes.

Where applicable, at timepoints coinciding with blood sample collection including PK, ECGs should be taken prior to blood collection and before vital sign measurements.

If a patient experiences Torsade de Pointes, additional concomitant PK samples (i.e., unscheduled) should be collected.

Table 4 Schedule for Triplicate ECG Collection

Cycle	Day	ECG timepoint (window)
Screening	-	Any time within 28 days prior to C1D1
C1	D1	Pre-dose (preferably within 2 h prior to start of infusion) EOI (within 10 min prior to EOI) Post-dose* 4 h (± 15 min)
	D8	Post-dose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (± 48 h; but within 30 min prior to PK sample)
C2	D1	Pre-dose (within 30 min prior to PK sample) EOI (within 10 min prior to EOI) Post-dose* 4 h (± 15 min)
	D8	Post-dose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (± 48 h; but within 30 min prior to PK sample)
C3	D1	Any time (but within 30 min prior to PK sample)
EOT		Any time (but within 30 min prior to PK sample)
Unscheduled		Any time

Abbreviations: ECG, electrocardiogram; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.
*Post-dose timepoint is counted from start of Loncastuximab tesirine infusion.

Eligibility and clinical decisions may be made based on the local ECG assessment. ECGs will be submitted for a central review. Submission instructions for the central review will be provided in a separate manual. Assessments will include determination of heart rate and rhythm and the PR, QRS, QT, QTcF), and QTcB intervals.

8.4 Pharmacokinetics, Pharmacodynamics, and Immunogenicity

PK, ADA, and [redacted] samples will be collected as per SoE (Table 1). Additional biological samples may be collected by the Investigator when clinically indicated (e.g., at the time of significant AEs that are at least possibly related to the study drug) and may be used for PK, pharmacodynamics, and/or [redacted] testing.

When multiple samples are required at the same timepoint, collection of safety samples should be first followed by PK, and then ADA.

In order to better understand the disease, metabolic disposition, and pharmacologic behavior of loncastuximab tesirine in humans, samples remaining after primary analyses may be utilized for further analysis.

Biological samples may be retained for up to 10 years to further address scientific questions as new information in regard to the disease or the study drug becomes available.

For detailed instructions related to central laboratory sample collection, labeling, processing, storage, or shipment refer to the appropriate laboratory manual(s).

8.4.1 Pharmacokinetics

The PK concentrations of loncastuximab tesirine (total antibody), PBD-conjugated antibody, and unconjugated warhead SG3199 will be assessed by a central laboratory designated by the Sponsor using validated bioanalytical methods.

Approximately 6 mL of whole blood will be collected as per Table 1 and Table 5. Blood should be drawn from a vein away from the one used for study drug infusion.

PK samples must be stored at -70°C. Please refer to the laboratory manual for detailed instructions regarding specimen handling and shipment.

PK blood collection should occur immediately after the end of the ECG recording and, when applicable, after vital signs. If a patient experiences Torsade de Pointes, additional PK samples (e.g., unscheduled) should be collected.

Table 5 Sampling Schedule for Loncastuximab Tesirine PK and ADA

Cycle	Day	PK timepoint (window)	ADA timepoint (window)
C1	D1	Pre-dose (preferably within 2 h prior to start of infusion) EOI (-5 to +10 min) Post-dose* 4 h (± 10 min)	Pre-dose (preferably within 2 h prior to start of infusion)
	D8	Post-dose* 168 h (± 48 h)	-
	D15	Post-dose* 336 h (± 48 h)	Post-dose* 336 h (± 48 h)
C2	D1	Pre-dose (within 2h prior to start of infusion) EOI (-5 to +10 min) Post-dose* 4 h (± 10 min)	Pre-dose (within 2 h prior to start of infusion)
	D8	Post-dose* 168 h (± 48 h)	-
	D15	Post-dose* 336 h (± 48 h)	-
C3	D1	Pre-dose (preferably within 2 h prior to start of infusion)	Pre-dose (preferably within 2 h prior to start of infusion)
C5, C6, C7**	D1	Pre-dose (preferably within 2 h prior to start of infusion)	Pre-dose (preferably within 2 h prior to start of infusion)
EOT		At any time during visit day	At any time during visit day
Unscheduled		Any time	Any time (if applicable, close to PK sample)

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.
*Post-dose timepoint is counted from start of loncastuximab tesirine infusion.
**Only for patients who receive loncastuximab tesirine during Cycles 5 and 6.

Blood samples for determination of durvalumab concentration in serum will be obtained according to the SoE, Table 1. The PK concentration of durvalumab prior to the C2D15 dose will also be assessed by a central laboratory designated by the Sponsor using a validated bioanalytical method.

To understand the metabolic disposition of loncastuximab tesirine in humans, samples remaining after PK analysis is complete may be pooled among patients for potential metabolite identification.

8.4.2 Immunogenicity

Detection of ADAs will be performed by using a screening assay for identification of antibody positive samples/patients, a confirmation assay, and titer assessment, and will be performed using the Meso-Scale Discovery Electrochemiluminescence (MSD-ECL) platform. If an ADA is confirmed, a functional assay for the assessment of the neutralizing capacity of the ADA will be performed.

Approximately 6 mL of whole blood will be collected as per Table 1 and Table 5. Blood should be drawn from a vein away from the one used for study drug infusion.

For patients who test positive for ADAs, an additional ADA sample will be requested for testing every 12 weeks following the EOT visit until the ADA titer falls to a background level.

ADA samples must be stored at ≤-70°C. Please refer to the laboratory manual for detailed instructions regarding specimen handling and shipment.

[redacted]

9 Statistical Considerations

Full details of the analysis plan, including a more technical and detailed elaboration of the statistical analyses, will be provided in the statistical analysis plan (SAP). [redacted]

9.1 Sample Size

The study will enroll approximately 75 patients. Part 1 (dose escalation) will enroll approximately 15 patients and Part 2 (dose expansion) will enroll approximately 60 patients (20 patients per cohort for up to 3 expansion cohorts, one for DLBCL, one for MCL and one for FL).

9.2 Analysis Populations

- The Safety analysis set consists of all patients who receive study drug.
- The DLT-evaluable analysis set consists of all patients in Part 1 who receive study drugs and excludes patients who discontinue from the study during the DLT period without experiencing a DLT.
- The Efficacy analysis set will consist of all patients who receive at least 1 dose of study drug, have valid baseline disease assessment(s), and at least one valid post-baseline disease assessment. Patients who do not have a post-baseline assessment due to early clinical progression or death (after receiving study drug) will also be included.
- PK Population: All patients with at least 1 pre- (C1D1) and 1 post-dose valid assessment.
- Pharmacodynamics Population: All patients with at least 1 valid pharmacodynamics/ [redacted] assessment.

9.3 Interim Analysis for Futility

No formal interim analysis is planned.

9.4 Final Analysis

All efficacy and safety endpoints will be analyzed and reported in the clinical study report (CSR).

9.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics, such as cancer history and medical history, will be summarized for the Safety analysis set.

9.6 Exposure to Treatments

Exposure to study drug and prior and concomitant medications will be summarized for the Safety analysis set. Dose interruptions, reductions, and relative dose intensity will also be summarized.

9.7 Efficacy Analyses

9.7.1 Overall Response Rate

The ORR will be defined as the proportion of patients with a BOR of CR or PR, according to the 2014 Lugano classification, as determined by the Investigator. The overall response category will be derived based on response assessment performed on or before the start of subsequent anti-cancer therapy.

The percentage of ORR with its 95% confidence interval (CI) will be presented. In contrast to CR, PR, or PD, a BOR of SD can only be made after the patient is on-study for a minimum of 35 days after the first dose of study drug. Any tumor assessment indicating SD before this time period will be considered as non-evaluable for BOR if no assessment after this time period is available.

9.7.2 Duration of Response

DOR will be defined among responders (CR or PR) as the time from the earliest date of first response until the first date of either disease progression or death due to any cause. For patients who have not progressed or died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. The data will be analyzed by the Kaplan-Meier method. The median duration of response and 95% CI will be presented. Further details will be outlined in the SAP.

9.7.3 Complete Response Rate

Complete response rate (CRR) will be defined as the proportion of patients with a BOR of CR, according to the 2014 Lugano classification, as determined by the Investigator. The percentage of CRR with its 95% CI will be presented.

9.7.4 Relapse-free Survival

RFS will be defined among CR patients as the time from the earliest date of first complete response until the first date of either disease progression or death due to any cause. For patients who have not progressed or died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. The data will be analyzed by the Kaplan-Meier method. The median RFS and 95% CI will be presented. Further details will be outlined in the SAP.

9.7.5 Progression-free Survival

PFS will be defined as the time from first dose of study drug until the first date of either disease progression or death due to any cause. For patients whose disease has not progressed at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. The data will be analyzed by the Kaplan-Meier method. The median PFS time and 95% CI will be presented. Further details will be outlined in the SAP.

9.7.6 Overall Survival

Median OS will be defined as the time from first dose of study drug until death due to any cause. For patients who have not died at the time of the analysis, censoring will be performed using the date the patient was last known to be alive. The data will be analyzed by the Kaplan-Meier method. The median OS and 95% CI will be presented. Further details will be outlined in the SAP.

9.8 Safety Analyses

Safety analyses will be presented descriptively.

9.8.1 Adverse Events

The focus of AE summarization will be on TEAEs. A TEAE is defined as an AE that occurs or worsens in the period extending from the first dose of study drug to 30 days after the last dose of study drug or initiation of new anti-cancer therapy (whichever occurs earlier).

TEAEs will be summarized. Summary tables will be presented to show the number of patients reporting TEAEs by severity grade and corresponding percentages. A patient who reports multiple TEAEs within the same Preferred Term (or System Organ Class [SOC]) is counted only once for that Preferred Term (or SOC) using the worst severity grade.

Separate summaries will be prepared for TEAEs classified as severe or life-threatening (Grade 3 or higher); study drug-related AEs; AEs leading to treatment interruption, modification, or discontinuation; serious AEs; and death.

9.8.2 Clinical Laboratory Results

Clinical hematology, coagulation panel, biochemistry, and urinalysis data will be summarized at each scheduled assessment. Shifts for clinical laboratory results that can be graded according to CTCAE v4.0 (or more recent) will be summarized by CTCAE grade. Shifts for other numeric laboratory results will be by high/normal/low flag. Shifts for all other laboratory results will be by normal/abnormal flag.

Summaries by visit will include data from scheduled assessments, and all data will be reported according to the nominal visit date for which it was recorded. Unscheduled data will be included in “worst-case post-Baseline” summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study drug. Further details will be provided in the SAP.

9.8.3 Additional Safety Assessments

The results of scheduled assessments of vital signs, physical examinations, ECOG performance status, and 12-lead ECGs will be summarized. All data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in "worst case" summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study drug. All data will be listed. Further details will be provided in the SAP.

9.9 Pharmacokinetic Analyses

The PK profile for loncastuximab tesirine in serum will include determination of maximum concentration (C_{max}), time to C_{max} (T_{max}), and area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$). [redacted]

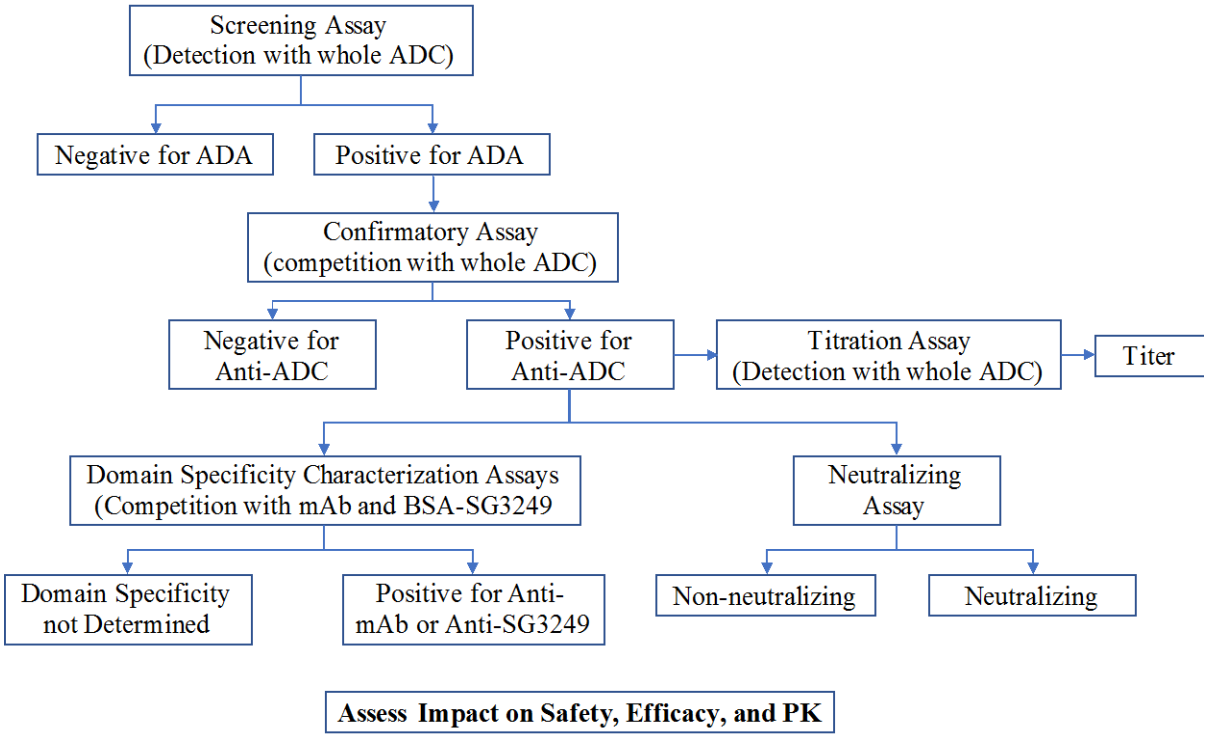
PK parameters will be determined for all PK-evaluable patients using either a compartmental (population) or non-compartmental analysis method with Phoenix WinNonlin [redacted] or other appropriate software and may be reported separately.

Demographic data for the PK population will be summarized. Potential correlations of PK parameters to baseline characteristics and safety observations will be assessed but may be reported separately. In addition, the influence of loncastuximab tesirine PBD-conjugated antibody and unconjugated warhead SG3199 concentrations, if appropriate on the QTc interval will be assessed but reported separately.

9.10 Immunogenicity Analyses

A tiered immunogenicity strategy (Figure 2) will be undertaken to evaluate ADAs by screening and confirmatory assays with titer evaluation, followed by characterization and evaluation of neutralizing capacity as needed. ADA sample collection, banking, and testing in validated and to be validated assays will be according to the new FDA Draft Guidance for Industry (April 2016): 'Assay Development and Validation for Immunogenicity testing of Therapeutic Protein Products'.

Figure 2 Anti-drug Antibody Tiered Immunogenicity Testing Strategy



Abbreviations: ADA, anti-drug antibody; ADC, antibody-drug conjugate; BSA, bovine serum albumin; mAb, monoclonal antibody; PK, pharmacokinetics.

Results from ADA testing will include tabular summarization for number/proportion of patients with positive pre-dose ADA response, number of patients with post-dose ADA response only, and number of patients with positive ADA response at any time. The denominator will be the total number of patients tested for ADAs in the study.

[redacted]

[redacted]

10 Data Management and Quality Assurance

The Investigator will maintain accurate source documentation including patient medical records, laboratory reports, ECG strips, and patient diaries.

Investigative site qualified personnel will enter patient data into an EDC system. The analysis data sets will be a combination of these data and data from other sources.

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

After database lock, each study site will receive information about all of their site-specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a copy of study data from all sites will be created and sent to the Sponsor for storage. The CRO will maintain a duplicate copy for its records. In all cases, patient initials will not be collected or transmitted to the Sponsor.

For detailed instruction on data entry procedures and timelines, please refer to the eCRF Completion Guidelines.

11 Ethical, Regulatory, and Study Management Considerations

11.1 Regulatory and Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and all applicable regulations.

11.2 Independent Ethics Committee or Institutional Review Board

Federal regulations and ICH guidelines require that approval be obtained from an Institutional Review Board (IRB)/IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study intended to be provided to the patient or the patient's legally authorized representative must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for obtaining continued review of the clinical research as specified by the IRB/IEC, at intervals not exceeding 1 year. The Investigator must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

11.3 Patient Information and Consent

Informed consent in compliance with IRB/IEC and local regulations shall be obtained from each patient or their legally authorized representative before performing any study procedures and will be documented with a signed IRB/IEC approved ICF. Before enrollment, each prospective patient or his or her legally authorized representative will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient/legally authorized representative understands the implications of participating in the study, the patient/legally authorized representative will be asked to give consent to participate in the study and sign the ICF. The process for obtaining consent has to be documented at the institution.

If the ICF is revised during the course of the study, all patients on-study, including those in follow-up, must sign the revised form, unless otherwise indicated by the IRB/IEC (local or global, as applicable). In such case, the reason for not re-consenting the patient should be documented.

11.4 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, regulatory authorities, or the IRB/IEC.

The Investigator and other study staff may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.5 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements as required under 21 CFR 54 and local regulations. In addition, the Investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

11.6 Serious Adverse Events Report Requirements

The Sponsor will ensure that all relevant safety information (SAEs and SUSARSs) is reported to the FDA and competent authorities of European Member States, and to the IRB/IEC, in accordance with current legislation.

11.7 Study Conduct

The Investigator will conduct all aspects of this study in accordance with the principles of the current version of ICH E6 as well as all national, state, and local laws and regulations. Study personnel involved in conducting this study will be qualified by education training and experience to perform their respective tasks. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of patients begins.

11.8 Protocol Amendments

Any change in the study plan requires a protocol amendment. All amendments to the protocol must be reviewed and approved following the same process as the original protocol before the amended protocol can be implemented. The Investigator will inform the governing IRB/IEC of all protocol amendments issued by the Sponsor in accordance with established IRB/IEC procedure. Only protocol amendments intended to eliminate an apparent immediate hazard to patient(s) may be implemented immediately, i.e., without IRB/IEC approval, but the circumstances of the change must be documented and submitted to the IRB/IEC.

11.9 Monitoring of the Study

All aspects of the study will be carefully monitored by the Sponsor or designee for compliance with GCP and applicable government regulations.

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency access to all study records.

The Investigator should promptly notify the Sponsor and the CRO of any inspections scheduled by any regulatory authorities and promptly forward copies of any inspection reports received to the Sponsor.

11.10 Records Retention

Essential documents should be retained for at least 15 years from the completion of the study (last patient last visit) or until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational study drug. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

11.11 Publications

Following completion of the study, the results from the study may be reported publicly by making any oral public presentation and/or submitting or presenting a manuscript, abstract, or other materials relating to the Study at scientific meetings and/or to a publisher, reviewer, or other outside person in scientific journals (“Publication”), provided; however, that Publication of the results from an individual site shall not be made before the first multi-site Publication by Sponsor. The Sponsor shall coordinate the drafting, editing, authorship, and other activities related to study Publication and shall mutually agree with the Investigator(s) on the number, medium, forum, and timing for Publication. The Sponsor shall solicit input regarding contents of the Publication from all Investigators and in consultation with all sites. The Sponsor acknowledges the right of the Investigator(s) to publish the results of this study after the entire study has completed, but also reserves the right to a window to review the Publication for regulatory compliance as well as for protection of its intellectual property. In particular, the Sponsor may request to remove the Sponsor’s confidential information and suspend Publication for a certain period of time to protect the Sponsor’s intellectual property interest, as further set forth in the Clinical Trial Agreement with the clinical study site(s) and Investigator(s).

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13 Appendices

13.1 Appendix 1 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG performance status grades as indicated below:

Grade	Definition
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, e.g., light house work, 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
Oken et al., 1982	

13.2 Appendix 2 Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (Lugano Classification)

Response / Site	PET-CT-Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response** (all of the following)
Lymph nodes and extralymphatic sites	• Score 1, 2, or 3* with or without a residual mass on 5PS**	• Target nodes/nodal masses must regress to ≤1.5 cm in LD
	Note: Uptake may be greater than normal mediastinum and/or liver in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors). 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	• No extralymphatic sites of disease
Nonmeasured lesion	• Not applicable	• Absent
Organ enlargement	• Not applicable	• Regress to normal
New lesions	• None	• None
Bone marrow	• No evidence of FDG-avid disease in marrow	• Normal by morphology; if indeterminate, [redacted]
Partial	**Partial metabolic response**	**Partial remission** (all of the following)

Response / Site	PET-CT-Based Response	CT-Based Response
Lymph nodes and extralymphatic sites	• Score 4 or 5** with reduced uptake compared with baseline and residual mass(es) of any size. • At interim, these findings suggest responding disease. • At end of treatment, these findings indicate residual disease.	• ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value • When no longer visible, 0 × 0 mm • For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	• Not applicable	• Absent/normal, regressed, but no increase
Organ enlargement	• Not applicable	• Spleen must have regressed by >50% in length beyond normal
New lesions	• None	• None
Bone marrow	• Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	• Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**

Response / Site	PET-CT-Based Response	CT-Based Response
Target nodes/nodal masses, extranodal lesions	• Score 4 or 5 with no significant change in FDG update from baseline at interim or end of treatment	• <50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	• Not applicable	• No increase consistent with progression
Organ enlargement	• Not applicable	• No increase consistent with progression
New lesions	• None	• None
Bone marrow	• No change from baseline	• Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease** (requires at least 1 of the following)
Individual target nodes/nodal masses	• Score 4 or 5 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 (e.g., a 15-cm spleen must increase to > 16

Response / Site	PET-CT-Based Response	CT-Based Response
		cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly
Nonmeasured lesions	• None	• New or clear progression of preexisting nonmeasured lesions
New lesions	• New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	• New or recurrent FDG-avid foci	• New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; [redacted]; 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 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 (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., 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 (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

** 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.
Cheson et al., 2014

13.3 Appendix 3 Guidelines for Durvalumab Dose Modification for Specific Immune-mediated Reactions

Adverse Events	Severity grade of the Event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients 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 modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 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/study regimen will be based upon treating	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt

		physician's clinical judgment and after completion of steroid taper.	treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still 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 (e.g., 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 (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., 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 study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to	

			infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** – 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). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or 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; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per

observations only)		treating physician's clinical judgment.
Grade 2 (Diarrhea: stool frequency of 4 to 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:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., 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 to 5 days or worsens despite prednisone at 1 to 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 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **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 study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

	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:** – 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 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., 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 the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB >ULN and ≤1.5×ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – 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:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly 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 work up and start prompt 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, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil 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 NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start

	and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	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 For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte

		imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – 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 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 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, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite

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

Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, 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 drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization.

		improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., 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**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., 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 (e.g., 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 (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
Grade 1	No dose modifications.	**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.
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.	**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

	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 (e.g., 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. 3. Doses of prednisone are ≤10 mg/day or equivalent.	endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., 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 (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.
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	**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

		completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., 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. 3. Doses of prednisone are ≤10 mg/day or equivalent.	empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., 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 (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**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 (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations).

		– Perform symptomatic treatment with neurological consult as appropriate. –
Grade 1	No dose modifications.	**For Grade 1:** – 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 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
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 study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Any Grade	**General Guidance**	**For Any Grade:**

Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients 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 (e.g., electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and

		followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
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 study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is 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. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV

		IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
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 or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:**	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist.

		Permanently discontinue study drug/study regimen.	○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
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 study physician. – 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 (e.g., 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 (e.g., disease progression, other medications, or infections).
Grade 1 (asymptomatic with laboratory (e.g., 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	- 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	**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

	or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	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.	complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., 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 (e.g., 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 (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
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 study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (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 (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult.

		– Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold 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 study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., 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 (e.g., 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 (refer to current NCCN guidelines for treatment of cancer-related infections

		[Category 2B recommendation]).[a]
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 study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., 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 IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

[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. AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; 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.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 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. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 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.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.