Official Title: A Phase Ib/II Open-Label, Multicenter Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Mosunetuzumab in Combination With Tiragolumab With or Without Atezolizumab in Patients With Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma

NCT Number: NCT05315713

Document Date: Protocol Version 4: 20-February-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE IB/II OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF MOSUNETUZUMAB IN COMBINATION WITH TIRAGOLUMAB WITH OR WITHOUT ATEZOLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMA**
PROTOCOL NUMBER:	CO43116
VERSION NUMBER:	4
ROCHE COMPOUNDS:	Mosunetuzumab (RO7030816), Tiragolumab (RO7092284), Atezolizumab (RO5541267), Tocilizumab (RO4877533)
STUDY PHASE:	Phase Ib/II
EUDRACT NUMBER:	2021-001060-23
IND NUMBER:	120651
NCT NUMBER:	NCT05315713
SPONSOR NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	See electronic date stamp on the final page.
3	24 April 2022
2	3 September 2021
1	11 March 2021

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol CO43116, Version 4, has been amended to update risks and safety management guidelines for mosunetuzumab, tiragolumab, atezolizumab, and tocilizumab to align with the most up to date Investigator's Brochures. Additional clarifications and changes to the protocol are summarized below:

- The synopsis has been simplified to align with the European Union Clinical Trial Regulation (CTR, Reg No 536/2014) and other guidelines.
- The health authority approval status for mosunetuzumab has been updated (Section 1.2).
- The collection of all serum anti-drug antibody (ADA) samples and study endpoints associated with ADAs for mosunetuzumab, tiragolumab, atezolizumab, and tocilizumab have been discontinued/removed in order to reduce patient sample collection burden given low utility of ADA analyses across development programs. In addition, pharmacokinetic (PK) samples for tocilizumab have been removed (Section 1.3 and Appendix 8).
- Additional language has been added to the Benefit–Risk Assessment section to emphasize that mosunetuzumab should not be administered in the presence of an active infection and to provide guidance on resuming treatment after a SARS-CoV-2 infection (Section 2.3.1 and A6–2.3.5).
- The association between ADAs and infusion-related reactions (IRRs) to tiragolumab has been removed because a low incidence of ADAs against tiragolumab and no association between ADAs and IRRs have been observed to date (Section 5.1.1.1).
- Additional language has been added in the Permitted Therapy (Infection Prophylaxis) section regarding recommendations on prophylaxis and prompt and maximized treatment of SARS-CoV-2 infection (Section 6.8.1.1).
- To reduce unnecessary sample collection, a statement was added to permit termination of sample collection by the Sponsor at any time. The decision to discontinue any sample collection will be communicated to sites (including Institutional Review Boards and Ethics Committees) by means of a memorandum and will not require a protocol amendment (Section 8).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (title page, front matter, and Section 8.3.10). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 8.10.2).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Roche practices (Section A1–4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority

databases for public access in addition to redacted Clinical Study Reports (Section A1–6).

- The Sponsor record retention policy has been clarified (Section A1–7).
- The guidance for how to re-start mosunetuzumab treatment after a dose delay has been updated so that only the step-up doses need to be repeated after a dose delay (5 mg on Day 1 and 45 mg on Day 8), but not the additional 45 mg dose on Day 15 of the first cycle after the treatment interruption (Section A6–2.2).
- For restarting study treatment following neurological adverse event resolution, it was clarified that decisions regarding potential dose reduction and schedule modifications will be made following individual benefit–risk assessment by the investigator and in consultation with the Medical Monitor. It was also clarified that Table A6–5 applies to both treatment- and non-treatment related management of neurological adverse events (Section A6–2.3.5).
- Tumor lysis syndrome prophylaxis recommendations were clarified to indicate that adequate hydration is required and administration of an agent to reduce uric acid should be considered (Section A6–2.3.6).
- The safety management guidance was amended to remove the sentence "Participants who demonstrate evidence of hepatitis reactivation will discontinue study treatment," which contradicts the guidance in Section A6–1.1.4 stating that continuation of treatment in patients who demonstrate evidence of hepatitis reactivation should be guided by benefit–risk assessment (Appendix 6–2.3.7).
- General guidance on how to assess and report a tumor flare event has been added to the safety section to help the investigator identify a tumor flare event following treatment with mosunetuzumab (Section A6–1.1.5 and A6–2.3.10).
- The safety management guidance was modified so that study treatment does not need to be held for Grade 1 or 2 thrombocytopenia, particularly if disease-related, in line with guidance from similar protocols (Appendix 6 and 7).
- To align with the Atezolizumab Investigator's Brochure, Version 19, and Addenda 1 and 2, updates have been made in several areas of the protocol, including Section 2.3, 5.2, 8.3.8, Appendix 6, and Appendix 13.
- To align with the Tiragolumab Investigator's Brochure, Version 7, the following changes have been made:
  - Immune-mediated hepatitis has been updated from a potential risk to an identified risk associated with tiragolumab and a new section describing the risk has been added (Section A6–1.3.2).
  - Examples of immune-mediated adverse events potentially associated with tiragolumab have been updated (Section A6–1.3.3).
  - Embryofetal toxicity has been added as a potential risk associated with tiragolumab (Section A6–1.3.4).
- Risk descriptions in the atezolizumab and/or tiragolumab adverse event management guidelines have been updated to align with the Atezolizumab

Investigator's Brochure, Version 19 and Tiragolumab Investigator's Brochure, Version 7 (Appendix 6).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE IB/II OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF MOSUNETUZUMAB IN COMBINATION WITH TIRAGOLUMAB WITH OR WITHOUT ATEZOLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMA**
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SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by Labcorp.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE: **A PHASE IB/II OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF MOSUNETUZUMAB IN COMBINATION WITH TIRAGOLUMAB WITH OR WITHOUT ATEZOLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMA**

STUDY RATIONALE

The purpose of this study is to assess the safety, efficacy, and pharmacokinetics of mosunetuzumab, a bispecific antibody targeting CD20 and CD3, in combination with tiragolumab, an anti-TIGIT (T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine based inhibition motif domains) antibody, with or without additional combination of atezolizumab, an antibody that targets PD-L1, in patients with relapsed or refractory (R/R) follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL). A proportion of patients with these diseases will be refractory to or will eventually relapse after the standard first-line chemoimmunotherapy, and relapses are characterized by increasing refractoriness and decreasing duration of response to subsequent lines of therapy. This underscores the need for novel treatments in subsequent lines of therapy that result in longer progression-free survival (PFS) and overall survival (OS) and have an improved benefit–risk profile. Mosunetuzumab is a T-cell–recruiting bispecific antibody, which leads to T-cell activation and target B-cell killing upon simultaneous binding to CD20 on B cells and CD3 on T cells.

Immune checkpoints consist of inhibitory and stimulatory pathways that maintain self-tolerance and assist with immune response. In cancer, immune checkpoint pathways are often activated to contribute to immune escape, leading to the persistence of cancer cells and resistance to therapy. In the microenvironment of non-Hodgkin lymphoma (NHL), T cells are frequently found expressing immune-inhibitory molecules, such as PD-1 and TIGIT, and TIGIT expression on T cells may be associated with advanced-stage disease in NHL. PD-1 and TIGIT are often co-expressed on lymphoma-infiltrating T cells. In a syngeneic murine B-cell lymphoma model, dual blockade of TIGIT and PD-1 drove more potent rejection of established lymphomas in mice than single blockade of either checkpoint, leading to the longer survival of the host. In addition, TIGIT-expressing T cells have impaired effector function in multiple myeloma samples, which can be reversed by TIGIT blockade. These findings suggest that TIGIT and PD-1 may be attractive targets of therapy in NHL.

Tiragolumab targets and blocks immune-inhibitory receptor TIGIT on immune effectors cells, thereby potentially restoring anti-tumor immunity through reversing the exhaustion of natural killer (NK) cells and increasing the immune activation of T_{eff} cells. Thus, combining tiragolumab with mosunetuzumab may further enhance the T cell recruitment, activation, and cytotoxicity mediated by mosunetuzumab. An addition of a third agent, atezolizumab, an anti–PD-L1 antibody, may further enhance immune-mediated tumor rejection by eliminating another pathway for immune escape. It is hypothesized that these doublet or triplet combinations may exert clinically meaningful anti-tumor activity in NHL.

OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of mosunetuzumab in combination with tiragolumab, with or without atezolizumab, in participants with R/R DLBCL or FL who have received at least two previous lines of systemic therapy.

Phase Ib–Specific Objectives	
Primary Objectives	
Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety of mosunetuzumab SC in combination with tiragolumab IV, including evaluation of the tolerability of the dosing schedule and dose, and characterization of DLTs in Cohort A and Cohort B • To evaluate the safety of mosunetuzumab SC with tiragolumab IV and atezolizumab IV, including evaluation of the tolerability of the dosing schedule and dose, and characterization of DLTs in Cohort E	• Incidence and severity of adverse events, including DLTs, with severity determined according to NCI CTCAE v5.0; for CRS, severity determined according to ASTCT CRS consensus grading criteria
Secondary Objectives	
Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the preliminary efficacy of mosunetuzumab SC in combination with tiragolumab IV in Cohorts A and B • To evaluate the preliminary efficacy of mosunetuzumab SC with tiragolumab IV and atezolizumab IV in Cohort E	• Best ORR (CR or PR at any time) in the study as determined by the investigator using Lugano 2014 criteria • Best CR rate, defined as the proportion of participants whose best overall response is a complete response during the study, as determined by the investigator using Lugano 2014 criteria • DOR, defined as the time from the first occurrence of a documented objective response (CR or PR) to disease progression or relapse, as determined by the investigator using Lugano 2014 criteria, or death from any cause, whichever occurs first
Phase II–Specific Objectives	
Primary Objectives	
Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV in participants with R/R FL (Cohort C) • To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV in participants with R/R DLBCL (Cohort D) • To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV in participants with FL (Cohort F)	• Best ORR, defined as the proportion of participants whose best overall response is a PR or a CR during the study, as determined by the investigator using Lugano 2014 criteria

Phase II–Specific Objectives (cont.)	
Secondary Objectives	
Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV in participants with R/R FL (Cohort C) • To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV in participants with R/R DLBCL (Cohort D) • To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV in participants with R/R FL (Cohort F)	• Best CR rate in the study, as determined by the investigator using Lugano 2014 criteria • DOR, defined as the time from the first occurrence of a documented objective response (CR or PR) to disease progression or relapse, as determined by the investigator using Lugano 2014 criteria, or death from any cause, whichever occurs first • PFS, defined as the time from the first study treatment to the first occurrence of disease progression or relapse, as determined by the investigator using Lugano 2014 criteria, or death from any cause, whichever occurs first • EFS, defined as the time from the first study treatment to the first occurrence of disease progression or relapse, as determined by the investigator using Lugano 2014 criteria, initiation of NALT, or death from any cause, whichever occurs first • OS, defined as the time from the first study treatment to death from any cause
Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety of mosunetuzumab in combination with tiragolumab in participants with R/R FL (Cohort C) • To evaluate the safety of mosunetuzumab in combination with tiragolumab in participants with R/R DLBCL (Cohort D) • To evaluate the safety of mosunetuzumab with tiragolumab and atezolizumab in participants with R/R FL (Cohort F)	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v5.0; for CRS, severity determined according to the ASTCT CRS Consensus Grading criteria
Objectives for Both Phase Ib and Phase II	
Secondary Objectives	
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the PK profile of mosunetuzumab SC in combination with tiragolumab IV (Cohort A, Cohort B, Cohort C, and Cohort D)	• C_{max} • C_{min} • Total exposure (AUC), CL, and volume of distribution, as estimated by population-PK modeling, as appropriate, and supported by data

Objectives for Both Phase Ib and Phase II (cont.)	
Secondary Objectives (cont.)	
Pharmacokinetic Objectives (cont.)	**Corresponding Endpoints (cont.)**
• To characterize the PK profile of mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV (Cohort E and Cohort F)	

ASTCT=American Society for Transplantation and Cellular Therapy; aTMTV=automated total metabolic tumor volume; AUC=area under the concentration-time curve; C_{max}=maximum concentration observed; C_{min}=minimum concentration observed; CR=complete response; CRS=cytokine release syndrome; CT=computed tomography; DLT=dose-limiting toxicity; DLBCL=diffuse large B cell lymphoma; DOR=duration of response; FL=follicular lymphoma; NALT=new anti-lymphoma treatment; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=objective response rate; PET=positron emission tomography; PR=partial response; R/R=relapsed or refractory; TMTV=total metabolic tumor volume.

OVERALL DESIGN

This is a Phase Ib/II, open-label, two-arm, multicenter study designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of mosunetuzumab SC in combination with tiragolumab IV with or without atezolizumab IV in participants with R/R B-cell NHL, specifically participants with DLBCL, HGBL, trFL, or FL (Grades 1–3b) who have received at least two prior lines of systemic therapy. A study schema and schedule of activities are available.

Participants will receive 8 cycles of study treatment, including all cycles in which at least one study drug is administered. Participants who achieve PR or SD at the time of primary response assessment (PRA) will continue treatment for a total of 17 cycles in the absence of disease progression.

Arm 1: mosunetuzumab SC in combination with tiragolumab IV—Safety Run-In Cohort A (initial) and Cohort B (alternate) will enroll approximately 6 participants with R/R DLBCL, HGBL, trFL, or R/R FL (Grade 1–3b) in each cohort. Following IMC recommendations on dosing, Expansion Cohort C will enroll approximately 40 participants with R/R FL (Grades 1–3a) and Expansion Cohort D will enroll approximately 40 participants with R/R DLBCL, HGBL, trFL, or R/R FL (Grade 3b).

- **Arm 2: mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV**—Safety Run-In Cohort E will enroll approximately 6 participants with R/R DLBCL, HGBL, trFL, or R/R FL (Grade1–3b). Following IMC recommendations on dosing, Expansion Cohort F will enroll approximately 20 participants with R/R FL (Grades 1–3a).

Several key aspects of the study design and study population are summarized below.

Phase:	*Phase Ib/II*	***Population Type:***	*Adult participants*
Control Method:	*None*	***Population Diagnosis or Condition:***	*R/R B-cell NHL*
Interventional Model:	*Sequential group*	***Population Age:***	*>18 years of age*
Test Compounds:	*Mosunetuzumab (RO7030816), Tiragolumab (RO7092284), Atezolizumab (RO5541267), Tocilizumab (RO4877533)*	***Site Distribution:***	*Multi-site*
Active Comparator:	*Not applicable*	***Study Intervention Assignment Method:***	*Open label*
Number of Arms:	*2*	***Number of Participants to Be Enrolled:***	*6–118*

STUDY TREATMENT

The investigational medicinal products for this study are mosunetuzumab SC, tiragolumab IV, atezolizumab IV, and tocilizumab IV.

DURATION OF PARTICIPATION

Treatment will continue for a total of 8 treatment cycles if a CR is achieved at PRA, or for 17 cycles if response is assessed as PR or SD at PRA as determined by the Lugano classification. Treatment will be discontinued if there is confirmed disease progression or unacceptable toxicity.

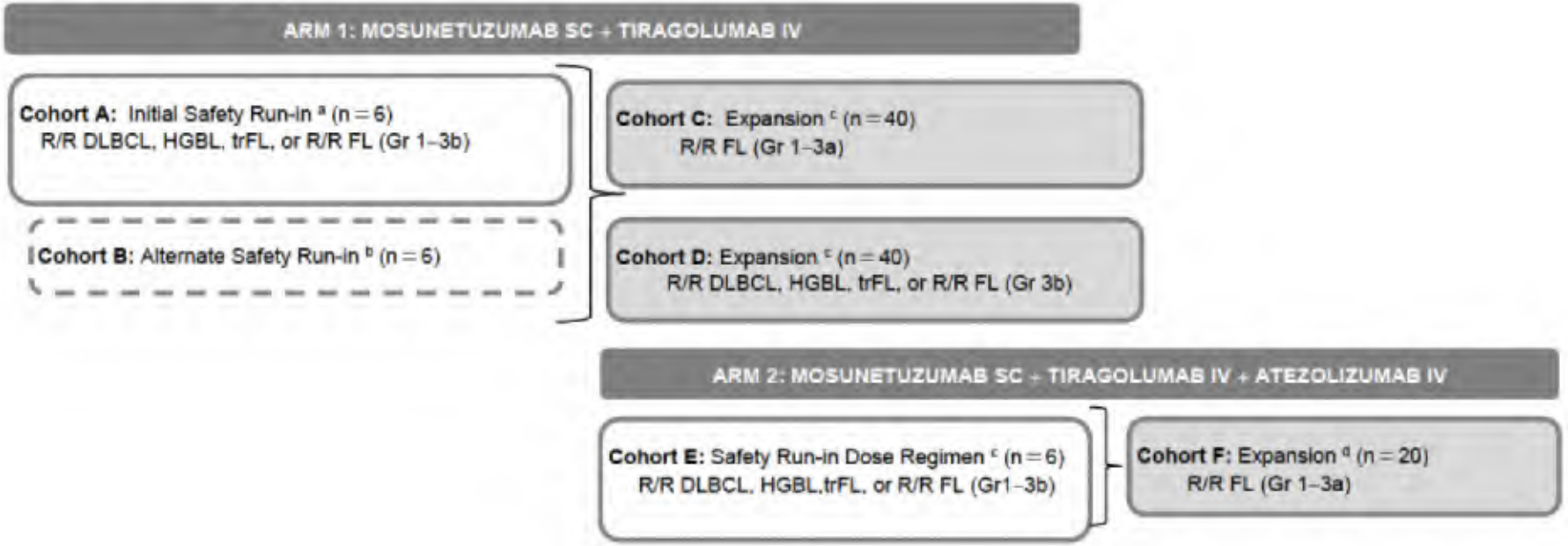
The total duration of study participation for each individual is expected to range from 1 day to more than 36 months.

COMMITTEES

Independent Committees:	*Not applicable*
Other Committees:	*Internal Monitoring Committee*

1.2 STUDY SCHEMA

Figure 1 Study Schema



DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; Gr = grade; HGBL = high grade B-cell lymphoma; IMC = Internal Monitoring Committee; RP2D = recommended Phase II dose; R/R = relapsed or refractory; trFL = transformed follicular lymphoma.

[a] For initial Safety Run-in Cohort A, the Cycle 1 Day 8 mosunetuzumab SC dose will be 45 mg (the RP2D as determined by Study GO29781).

[b] Refer to the alternate Safety Run-In dose regimen for Cohort B displayed in Figure 3.

[c] Expansion Cohorts C and D will proceed per the IMC recommendation. The combination mosunetuzumab SC + tiragolumab IV dose and regimen in Cohorts C, D, E and F will be the RP2D combination dose from the Safety Run-In. Cohort E will open as per Section 9.5.

[d] Expansion Cohort F will proceed per the IMC recommendation.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

Day(s) (Window in days)	SCR [a] −14 to −1	Cycle 1				Cycle 2			Cycle 3	Cycle 4	IRA	Cycle 5–8 (−17) [b]	PRA	Tx Comp/ Early Discon [c]	Long-Term FUP [d]
		D1 [y]	D2 [e]	D8 [y] (±1)	D15 [y] (±1)	D1 [y] (±1)	D2 [e]	D8 [e] (±1)	D1 [y] (±2)	D1 [y] (±2)	Cycle 4 D15–21	D1 [y] (±2)	Cycle 8 D15–21		
Informed consent [f]	x [f]														
Demographics	x														
Medical history and baseline conditions	x														
ECOG Performance Status	x	x				x			x	x		x			
Vital signs [g]	x	x [g]	x [e]	x [g]	x [g]	x [g]	x [e]	x [e]	x [g]	x [g]		x [g]		x	
Weight	x	x												x	
Height and BSA	x														
Complete physical examination [h]	x													x	
Targeted physical examination [i]		x	x [e]	x	x	x		x [e]	x	x		x			
Concomitant medications [j]	x [j]	x	x [e]	x	x	x		x [e]	x	x		x		x	
Adverse events [k]	x [k]	x	x [e]	x	x	x	x [e]	x [e]	x	x	x	x	x	x [k]	
Single 12-Lead ECG	x													x	
Hematology [l, y]	x	x		x	x	x		x [e]	x	x		x		x	
Chemistry [m, y]	x	x		x	x	x		x [e]	x	x		x		x	
LDH [y]	x	x		x	x	x		x [e]	x	x		x		x	
Amylase and Lipase	(x) [n]														

Table 1 Schedule of Activities (cont.)

Day(s) (Window in days)	SCR [a] −14 to −1	Cycle 1				Cycle 2			Cycle 3	Cycle 4	IRA	Cycle 5–8 (−17) [b]	PRA	Tx Comp/ Early Discon [c]	Long-Term FUP [d]
		D1 [y]	D2 [e]	D8 [y] (±1)	D15 [y] (±1)	D1 [y] (±1)	D2 [e]	D8 [e] (±1)	D1 [y] (±2)	D1 [y] (±2)	Cycle 4 D15–21	D1 [y] (±2)	Cycle 8 D15–21		
Thyroid Function Tests (TSH and free T4)	x											(x) [o]		x	
C-reactive protein (CRP) and serum ferritin [y]	x	x		x	x	x			x	x					
Coagulation	x														
HBV, HCV, and HIV [p]	x														
EBV and CMV [p, y]	x [q]					x [q]									
Quantitative immunoglobulins (IgA, IgG, IgM)	x											(x) [o]		x	x [r]
Pregnancy test [s]	x	x				x			x	x		x		x	(x) [s]
Tumor assessment [t]	x										x	(x) [t]	x		(x) [t]
Bone Marrow Biopsy and Aspirate [u]	(x) [u]										(x) [u]				
Tumor tissue, blood, plasma, and PBMC for biomarkers	See Table 2 and Table 3 for the biomarker sampling schedule														
(Optional) Additional fresh/repeat biopsy	See Table 2 and Table 3 for the optional biopsy sampling schedule														
Serum PK sample	See Table 2 and Table 3 for the PK sampling schedule														
(Optional) Blood sample for RBR	See Table 2 and Table 3 for the RBR sampling schedule														
Survival and anti-cancer therapy follow-up														x	(x) [d]
Corticosteroid prophylaxis [v]		x		x	x	(x)			(x)	(x)		(x)			

Table 1 Schedule of Activities (cont.)

Day(s) (Window in days)	SCR [a] −14 to −1	Cycle 1				Cycle 2			Cycle 3	Cycle 4	IRA	Cycle 5–8 (−17) [b]	PRA	Tx Comp/ Early Discon [c]	Long-Term FUP [d]
		D1 [y]	D2 [e]	D8 [y] (±1)	D15 [y] (±1)	D1 [y] (±1)	D2 [e]	D8 [e] (±1)	D1 [y] (±2)	D1 [y] (±2)	Cycle 4 D15–21	D1 [y] (±2)	Cycle 8 D15–21		
Study Drug Administration [w]															
Cohort A															
Mosunetuzumab administration		x		x	x	x			x	x		x			
Tiragolumab administration		x				x			x	x		x			
Cohort B															
Mosunetuzumab administration		x		x	x	x			x	x		x			
Tiragolumab administration						x			x	x		x			
Cohorts C and D															
Mosunetuzumab administration		x		x	x	x			x	x		x			
Tiragolumab administration		(x) [x]				x			x	x		x			
Cohorts E and F															
Mosunetuzumab administration		x		x	x	x			x	x		x			
Tiragolumab administration		(x) [x]				x			x	x		x			
Atezolizumab administration						x			x	x		x			

Table 1 Schedule of Activities (cont.)

BSA=body surface area; C=cycle; CMV=cytomegalovirus; Comp=completion; CT=computed tomography; D=day; DC=discontinue; EBV=Epstein-Barr virus; eCRF=electronic Case Report Form; FUP=follow-up; IRA=interim response assessment; LDH=lactate dehydrogenase; NA=not applicable; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; PR=partial response; PRA=primary response assessment; RBR=Research Biosample Repository; Scr=screening; SD=stable disease; UV=unscheduled visit; WES=whole exome sequencing; WGS=whole genome sequencing, (x)=conditional or optional (refer to footnote).

Notes: Assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

Unscheduled visits may be performed if clinically indicated. Participants will undergo the specified assessments, and additional assessments may be performed if clinically indicated, as determined by the investigator.

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and within 14 days prior to C1D1 may be used; such assessments do not need to be repeated for screening. Radiographic tumor assessments obtained during 28 days prior to C1D1 will be acceptable, and bone marrow examinations (if applicable) obtained up to 90 days prior to C1D1 will be acceptable, provided that no anti-tumor therapy was administered during the respective period. Individuals who do not meet the criteria for participation in this study may qualify for 2 re-screening opportunities (for a total of 3 screenings per individual) at the investigator's discretion, as described in Section 5.4.

[b] Participants will receive 8 cycles of study treatment, including all cycles in which at least one study drug is administered. Participants who achieve PR or SD at the time of PRA will continue treatment for a total of 17 cycles in the absence of disease progression.

[c] Participants who complete the treatment period will return to the clinic for a treatment completion visit 30 (±7) days after their final dose of study drug. Participants who discontinue study treatment prematurely will return to the clinic for a treatment discontinuation visit 30 (±7) days after their final dose of study drug. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[d] After treatment discontinuation, information on survival status and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death (unless the participant withdraws consent or the Sponsor terminates the study). If a participant requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[e] Visit applicable for participant in a Safety Run-In Cohort and may be omitted for participants in an Expansion Cohort. Assessments designated for Day 2 during Cycle 1 and Cycle 2 are only applicable for participants who are hospitalized (see Section 4.4) or if the participant returns for a scheduled outpatient visit as part of standard of care.

[f] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained no more than 14 days before initiation of study treatment.

[g] Vital signs include temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure. Blood pressure and pulse rate will be measured while the participant is in a seated or semi-supine position after 5-minutes rest. Vital signs should be assessed prior to mosunetuzumab injection (within 30 minutes prior to injection) and after administration of each study drug. See Section 6.1.1 for guidance on vital sign recording after mosunetuzumab injection. See Section 6.1.2 (Table 6) and Section 6.1.3 (Table 7) for information on recording vital signs before and after administration of tiragolumab or atezolizumab.

[h] A complete physical examination includes, at a minimum, assessments of the cardiovascular, dermatologic, musculoskeletal, respiratory,

Table 1 Schedule of Activities (cont.)

gastrointestinal, and neurologic systems; enlarged lymph nodes, hepatomegaly, splenomegaly, or other findings of concern for lymphoma should be evaluated; genitourinary exams may be performed if clinically indicated.

[j] Targeted physical examination includes, at a minimum, assessments of the skin, respiratory and cardiovascular systems, and abdomen (liver and spleen) and findings of concern for lymphoma. Investigators should pay special attention to clinical signs related to previous serious illnesses.

[k] Concomitant medications includes any medication or vaccine (including over-the-counter or prescription medicines, vitamins, or herbal supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the study completion/discontinuation visit.

[l] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 90 days after the final dose of study treatment. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study drug (see Appendix 3).

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, absolute neutrophil count, absolute lymphocyte count, and other cells (see Appendix 2).

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, magnesium, total and direct bilirubin, albumin, ALP, ALT, AST, gamma-glutamyl transpeptidase, and uric acid (see Appendix 2).

[o] Atezolizumab-treated participants only (Cohorts E and F).

[p] Cycles 5, 9, and 13.

[q] See Appendix 2.

[r] EBV to be performed at Screening and C2D1. Positive results require continued monitoring of viral load weekly until down-trending, every cycle until undetectable viral load.

[s] Collect every 6 months during long-term follow-up.

[t] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study treatment. Urine pregnancy tests will be performed on Day 1 of each treatment cycle and at the treatment discontinuation visit, and at 3 months after the final dose of study treatment, plus an additional test at 5 months after the final dose of atezolizumab, if applicable. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[u] FDG PET–CT scans, in conjunction with diagnostic-quality CT scans, are required at screening, IRA, and PRA. After PRA, response will continue to be evaluated by CT scans with or without PET every 3 months during the first year after treatment initiation, and then every 6 months until the participant develops progressive disease, study discontinuation, and/or the start of new lymphoma treatment, or at any time disease progression is suspected. See Section 8.1.1 and Section 8.1.1.1.

Table 1 Schedule of Activities (cont.)

[u] Participants with DLBCL may use screening PET/CT scans to assess bone marrow involvement; bone marrow examinations are not required unless clinically indicated. Participants with FL or trFL who had bone marrow infiltration at any time prior to study initiation are required to undergo bone marrow examinations at screening (within 90 days prior to initiation of study treatment) for staging purposes. Participants with FL or trFL are required to undergo repeat bone marrow examinations to confirm the first radiologic assessment of CR within 42 days if there was tumor-infiltrated bone marrow at screening and to confirm suspected relapse in the bone marrow. See Section 8.1.1.2.

[v] Dexamethasone 20 mg (preferred) or methylprednisolone 80 mg should be administered orally or intravenously prior to the administration of each mosunetuzumab dose. Regarding the use of an alternative corticosteroid compound of equal corticosteroid potency (e.g., due to unavailable dexamethasone or methylprednisolone), the Medical Monitor should be consulted. The administration of corticosteroid premedication may be optional for Cycle 2 and beyond based on the investigator's assessment. However, if the participant experiences CRS with prior administration of mosunetuzumab, premedication with steroids must be administered for subsequent doses until no additional CRS events are observed. Please also see Section 6.1.1 for guidance on steroid prophylaxis.

[w] For participants receiving re-treatment, if the treatment-free interval is less than 6 weeks, participants should start with the Cycle 2 schedule of assessments.

[x] Cohorts C, D, E, and F will use the dose schedule for mosunetuzumab and tiragolumab determined during the Safety Run-In of Arm 1.

[y] On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Pre-treatment laboratory samples for blood chemistry, hematology, LDH, EBV, CMV, CRP, and serum ferritin should be drawn 0–36 hours prior to dosing.

Table 2 Cycle 1 and Cycle 2: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

		Cycle 1								Cycle 2					
		D1			D2	D4	D8	D15		D1			D2	D4	D15–D21
	Scr	Pre-Tx [a]	30 m Post-Tx [b]	3 h Post-Tx [b]	24 h Post-Tx [b]	72 h Post-Tx [b]	Pre-Tx [a]	Pre-Tx [a]	D15–D21	Pre-Tx [a]	30 m Post-Tx [b]	3 h Post-Tx [b]	24 h Post-Tx [b]	72 h Post-Tx [b]	
Window	−14 to −1	−8–0 h	±10 min	±15 min	±6 h	±6 h	−8–0 h	−8–0 h		−8–0 h	±10 min	±15 min	±6 h	±6 h	
Plasma for biomarkers		x	x	x	(x) [c, d]	(x) [c, d]		x		x	x	x	(x) [d, e]	(x) [d, e]	
Blood for flow cytometry		x			(x) [c, d]			(x) [c]		x			(x) [d, e]		
Blood for TBNK		x								x					
PBMCs for biomarkers		x						(x) [f]		x					(x) [f]
RBR (optional)		(x) [g]													
Fresh (or archive) tumor tissue sample for biomarkers (mandatory)	x [h]														
Fresh tumor tissue sample for biomarkers (optional paired)	(x) [i]								(x) [c, i]						(x) [e, i]

Table 2 Cycle 1 and Cycle 2: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

		Cycle 1								Cycle 2					
		D1			D2	D4	D8	D15		D1			D2	D4	D15–D21
	Scr	Pre-Tx [a]	30 m Post-Tx [b]	3 h Post-Tx [b]	24 h Post-Tx [b]	72 h Post-Tx [b]	Pre-Tx [a]	Pre-Tx [a]	D15–D21	Pre-Tx [a]	30 m Post-Tx [b]	3 h Post-Tx [b]	24 h Post-Tx [b]	72 h Post-Tx [b]	
Window	−14 to −1	−8–0 h	±10 min	±15 min	±6 h	±6 h	−8–0 h	−8–0 h		−8–0 h	±10 min	±15 min	±6 h	±6 h	
Serum for mosunetuzumab PK		x		(x) [c]	(x) [c, d]	(x) [c, d]	x	x		x		(x) [e]	(x) [d, e]	(x) [d, e]	
Serum for tiragolumab PK		(x) [c]	(x) [c]	(x) [c]	(x) [c, d]		(x) [c]	(x) [c]		x	x	(x) [e]	(x) [d, e]		
Serum for atezolizumab PK		(x) [i]								(x) [i]		(x) [i]	(x) [d, i]		
Serum for obinutuzumab PK		x													
Serum for rituximab PK		x													

Table 2 Cycle 1 and Cycle 2: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

D = Day; h = hour; FFPE = formalin-fixed, paraffin-embedded; m = minute; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RBR = Research Biosample Repository; Scr = screening; TBNK = T-cell, B-cell, and natural killer cell; Tx = treatment; (x) = conditional/optional (see footnote).

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

Expansion Cohort C, Cohort D, and Cohort F biomarker collections are to be aligned with the combination mosunetuzumab + tiragolumab dose schedule determined during the Safety Run-In.

[a] Collect pretreatment samples −8–0 hours prior to administration of the first study drug.

[b] Collect post-treatment samples at 30 min, 3 hours, 24 hours (for hospitalized participants), and 72 hours (for hospitalized participants) after the completion of the tiragolumab infusion for applicable participants.

[c] Collect samples for participants in Cohort A and Cohort E (if receiving tiragolumab in Cycle 1).

[d] Only applicable to patients in Safety Run-In that are hospitalized.

[e] Collect samples for participants in Cohort B and E.

[f] Collect PBMC sample at C1D15 (or at the time of optional on-treatment biopsy collection, C1D15–C2D1) and/or C2D15 (or at the time of optional on-treatment biopsy collection, C2D15-C3D1).

[g] With consent to optional research, a blood sample will be requested at baseline for collection and storage at the RBR.

[h] See Section 8.7 for details. A mandatory pretreatment biopsy is required. Nodal biopsies are preferred to bone marrow aspirates/biopsies. The pretreatment biopsy (fresh or archival) should be obtained, preferably after the most recent prior therapy and before initiation of mosunetuzumab treatment. If a pretreatment biopsy cannot be performed, an archival tumor sample must be made available to the Sponsor. Archival biopsy samples must be accompanied by the associated pathology report; the pathology report for fresh samples may be sent when available. Tumor tissue samples should consist of representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides.

[i] Optional fresh paired biopsies at baseline, on-treatment and on-progression are requested to perform single-cell trancriptomics from all patients. Obtain a fresh biopsy at baseline and an on-treatment biopsy (C1D15–C1D21 or C2D15–C2D21 based on the schedule determined from the Safety Run-In from the same lesion. If this is not possible then a biopsy may be obtained from another safely accessible site. Paired biopsies for single cell transcriptomics should be collected and flash frozen. If a fresh, flash frozen baseline biopsy is not obtained at baseline, then any second biopsy should not be collected as FFPE.

[j] Collect samples for participants in Cohort E and F.

Table 3 Cycle 3–Cycle 16, Study Treatment Completion/Early Discontinuation and Follow-Up: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

	Cycle 3	Cycle 4		Cycle 5	Cycle 8		Cycle 12	Cycle 16		
	D1	D1		D1	D1		D1	D1		
	Pre-Tx [a]	Pre-Tx [a]	3 h Post-Tx [b]	PreTx [a]	Pre-Tx [a]	PRA	Pre-Tx [a]	Pre-Tx [a]	Tx Comp/ Early Discon	FUP
Window	−8–0 h	−8–0 h	±15 min	−8–0 h	−8–0 h	D15–21		−8–0 h		
Plasma for biomarkers	x									
Blood for flow cytometry	(x) [c]								x	
Blood for TBNK		x			x					x [d]
PBMCs for biomarkers		x			x				x	
Fresh tumor tissue sample for biomarkers									(x) [e]	
Serum for mosunetuzumab PK	x	x	x	x	x	x		x	x	x [g]
Serum for tiragolumab PK	x	x	x	x	x	x	x	x	x	x [g]
Serum for atezolizumab PK	(x) [f]	(x) [f]	(x) [f]	(x) [f]	(x) [f]	(x) [f]	(x) [f]	(x) [f]	(x) [f]	(x) [f, g]

D = Day; FUP = follow-up; h = hour; m = minute; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; PRA = primary response assessment; RBR = Research Biosample Repository; Scr = screening; TBNK = T-cell, B-cell, and natural killer cell; Tx = treatment; (x) = conditional/optional (refer to footnote).

Note: Expansion Cohort C, Cohort D and Cohort F biomarker collections are to be aligned with the combination dose schedule determined during the Safety Run-In.

[a] Collect pretreatment samples –8–0 hours prior to administration of the first study drug.

[b] Collect post-treatment samples at 3 hours after the completion of the tiragolumab infusion.

[c] Collect samples for participants in Cohort B and E.

[d] Collect sample for TBNK every 3 months for up to 2 years after completion or discontinuation from the study treatment, or until disease progression.

Table 3 Cycle 3–Cycle 16, Study Treatment Completion/ Early Discontinuation and Follow-Up: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

[e] Optional fresh paired biopsies at baseline, on-treatment and on-progression are requested to perform single-cell trancriptomics. Obtain a fresh biopsy at baseline and an on-treatment biopsy (C1D15–C2D1 or C2D15–C3D1 based on the schedule determined from the Safety Run-In) from the same lesion. If this is not possible then a biopsy may be obtained from another safely accessible site. If a fresh baseline biopsy is not obtained at baseline, then a second biopsy should not be collected.

[f] Collect samples for participants in Cohort E and F.

[g] Collect sample ≥90 days after last study drug administration for patients in follow up.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the safety, efficacy, and pharmacokinetics of mosunetuzumab, a bispecific antibody targeting CD20 and CD3, in combination with tiragolumab, an anti–T-cell Immunoreceptor with Immunoglobulin and Immunoreceptor Tyrosine-Based Inhibition Motif domains (TIGIT) antibody, with or without additional combination of atezolizumab, an antibody that targets PD-L1, in patients with relapsed or refractory (R/R) follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL). A proportion of patients with these diseases will be refractory to or will eventually relapse after the standard first-line chemoimmunotherapy, and relapses are characterized by increasing refractoriness and decreasing duration of response to subsequent lines of therapy. This underscores the need for novel treatments in subsequent lines of therapy that result in longer progression-free survival (PFS) and overall survival (OS) and have an improved benefit–risk profile. Mosunetuzumab is a T cell-recruiting bispecific antibody, which leads to T-cell activation and target B-cell killing upon simultaneous binding to CD20 on B cells and CD3 on T cells.

Immune checkpoints consist of inhibitory and stimulatory pathways that maintain self-tolerance and assist with immune response. In cancer, immune checkpoint pathways are often activated to contribute to immune escape, leading to the persistence of cancer cells and resistance to therapy. In the microenvironment of non-Hodgkin lymphoma (NHL), T cells are frequently found expressing immune-inhibitory molecules, such as PD-1 and TIGIT, and TIGIT expression on T cells may be associated with advanced-stage disease in NHL (Josefsson et al. 2019). PD-1 and TIGIT are often co-expressed on lymphoma infiltrating T cells. In a syngeneic murine B cell lymphoma model, dual blockade of TIGIT and PD-1 drove more potent rejection of established lymphomas in mice than single blockade of either checkpoint, leading to the longer survival of the host (Sunseri et al. 2019). In addition, TIGIT-expressing T cells have impaired effector function in multiple myeloma samples, which can be reversed by TIGIT blockade (Guillerey et al. 2018). These findings suggest that TIGIT and PD-1 may be attractive targets of therapy in NHL.

Tiragolumab targets and blocks immune-inhibitory receptor TIGIT on immune effectors cells, thereby potentially restoring anti-tumor immunity through reversing the exhaustion of natural killer (NK) cells and increasing the immune activation of T_{eff} cells. Thus, combining tiragolumab with mosunetuzumab may further enhance the T-cell recruitment, activation, and cytotoxicity mediated by mosunetuzumab. An addition of a third agent, atezolizumab, anti–PD-L1 antibody may further enhance immune-mediated tumor rejection by eliminating another pathway for immune escape. It is hypothesized that these doublet or triplet combinations may exert clinically meaningful anti-tumor activity in NHL.

2.2 BACKGROUND

Indolent B-cell malignancies like FL, as well as approximately half of all aggressive lymphomas, which include DLBCL and transformed FL (trFL), remain incurable despite advances in immunochemotherapy that have resulted in longer PFS (Coiffier et al. 2002; Feugier et al. 2005; Hiddemann et al. 2005; Vidal et al. 2012). Moreover, given that NHL is frequently diagnosed in older patients, the ability to tolerate cytotoxic chemotherapy is a major barrier to treatment success. Consequently, there remains a need for patients who do not respond to or relapse after standard chemoimmunotherapy to develop novel treatments that may significantly extend disease-free survival and OS, while providing acceptable, if not superior, safety and tolerability.

Recent developments support the effectiveness of therapies that utilize T cells in the treatment of B-cell malignancies. The approach to redirect T cells to target lineage-specific surface molecules such as CD19 has shown potent clinical activity in patients with R/R NHL, either by genetically modifying T cells to express chimeric antigen receptors (CARs) or by administration of bispecific molecules that simultaneously bind CD3 and the target antigen (Bargou et al. 2008; Kochenderfer et al. 2012; Grupp et al. 2013; Viardot et al. 2016).

Mosunetuzumab (RO7030816; BTCT4465A), is a full length, humanized anti-CD20/CD3 bispecific IgG1 antibody engineered for minimal binding to Fcγ receptors (Atwell et al. 1997; Spiess et al. 2013). CD20 is a validated target in B-cell NHL, which provides a rationale for the development of a T cell–recruiting bispecific antibody targeting CD20 for treatment of these diseases. Mosunetuzumab has shown promising single-agent activity in indolent and aggressive NHL and a manageable safety profile. There remains a need to increase remission rates and survival while preserving the beneficial benefit–risk profile. *Mosunetuzumab (Lunsumio®) as monotherapy via intravenous infusion has been conditionally approved by the U.S. Food and Drug Administration (FDA) and European Commission for the treatment of adult patients with R/R FL who have received at least two prior systemic therapies. Clinical development is ongoing for additional indications. Refer to local prescribing information for further details of approved use.*

Tiragolumab is a fully human IgG1/kappa monoclonal antibody that binds TIGIT and prevents its interaction with CD155. TIGIT is an inhibitory immunoreceptor that is expressed on subsets of activated T cells and NK cells and found highly expressed in tumor tissue and in tumor-infiltrating immune cells in many human cancers, including NHL. Its expression is associated with impaired immune cell function and anti-tumor immunity (Johnston et al. 2014; Bachanova et al. 2018; Josefsson et al. 2019). For patients with DLBCL who have been treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone therapy, low NK-cell counts at diagnosis are associated with poor clinical outcomes (Kim et al. 2014). In addition to potentially activating exhausted NK cells seen from preclinical models, tiragolumab has

also been shown to enhance T_{eff} function and counter T_{reg}-mediated immune suppression (Stanietsky et al. 2009; Johnston et al. 2014; Kurtulus et al. 2015). The data support the hypothesis that anti-TIGIT may enhance anti-tumor immunity in hematologic malignancies to provide clinical benefit to patients.

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1, both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab shows anti-tumor activity in cancer patients and is being investigated as a single agent, or in combination with chemotherapy, targeted therapy, and cancer immunotherapy, in a wide variety of malignancies. Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, and melanoma. Treatment with T-cell–recruiting bispecific molecules results in transient elevations in cytokine levels including interferon gamma (IFN-γ), which has been demonstrated to induce PD-L1 expression on tumor cells which inhibit T-cell effector function (Blank et al. 2004). In the A20-huCD20 mouse B-lymphoma model, which was shown to have high levels of PD-L1 expression, treatment with the 2H7v16/2C11 antibody (a surrogate anti–CD20/CD3 antibody with the same clone of anti–human CD20 (2H7v16) as in mosunetuzumab paired with anti–murine CD3 clone 2C11) alone did not inhibit tumor growth. Treatment with the anti–PD-L1 antibody alone induced tumor regression or growth inhibition in 30% of the animals. In contrast, treatment with the combination of 2H7v16/2C11 and anti–PD-L1 antibodies resulted in tumor regression or tumor growth inhibition in all tested animals (Sun et al. 2016). These results indicated that PD-L1 expression on target A20-huCD20 B-lymphoma cells may inhibit the anti-tumor activity of 2H7v16/2C11, and concomitant blockade of PD-L1 can overcome this inhibition and render the tumor cells susceptible to enhanced 2H7v16/2C11–mediated killing. In vitro assays in human peripheral blood mononuclear cells (PBMCs) showed that mosunetuzumab treatment induced PD-L1 upregulation on target B cells, as well as greater percentage of PD-L1+ B cells, likely mediated by cytokines such as IFN-γ (Sun et al. 2016). These observations suggest that mosunetuzumab administration in patients can induce PD-L1 upregulation, potentially impacting the efficacy of single-agent mosunetuzumab, and further supports combining mosunetuzumab with an anti–PD-L1 antibody.

Detailed information on mosunetuzumab, tiragolumab, and atezolizumab is provided in the respective Investigator's Brochures.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the safety, pharmacokinetics, and efficacy of mosunetuzumab in combination with tiragolumab, with or without additional combination

with atezolizumab, to address a significant unmet medical need in patients with R/R NHL.

Mosunetuzumab is a T cell–dependent bispecific antibody that has shown single-agent activity in a Phase Ib clinical trial (Study GO29781) in both indolent and aggressive NHL. TIGIT and PD-1 expression levels are elevated in the tumor microenvironment in many human tumors, including NHL, are associated with impaired T-cell function and are therefore potential targets for therapeutic intervention aimed at enhancing the anti-tumor immune response. Consequently, there is potential that the combination of mosunetuzumab with the TIGIT inhibitor tiragolumab enhances the immune response in NHL and leads to improved outcomes, which could further be improved by additional combination with the PD-L1 inhibitor atezolizumab.

Mosunetuzumab has shown an acceptable safety profile as monotherapy and in combination with atezolizumab in Study GO29781. The following are identified and potential risks for mosunetuzumab, based on its mechanism of action, available nonclinical and clinical data, data from other T cell–engaging therapeutics, and general risks associated with biologic agents: cytokine-release syndrome (CRS) or infusion-related reactions (IRRs), neutropenia, local injection-site reactions, tumor lysis syndrome (TLS), tumor flare, infections, neurologic adverse events, hemophagocytic lymphohistiocytosis (HLH), thrombocytopenia, elevated liver enzymes, and immunogenicity (anti-drug antibodies [ADAs]).

Tiragolumab has shown a tolerable safety profile as a monotherapy and in combination with rituximab for patients with NHL in Study GO41036. *Infusion-related reactions and immune-mediated hepatitis are identified risks of tiragolumab.* On the basis of clinical experience with tiragolumab given as a single agent and in combination with atezolizumab, no maximum tolerated dose (MTD), no dose limiting toxicities (DLTs), and no clear dose-related trends in the incidence or severity of adverse events have been seen in the Phase Ia/Ib study in solid tumors (Study GO30103). The safety profile of tiragolumab given as a single agent and in combination with atezolizumab is observed to be consistent across different solid tumor indications (as assessed in non–small cell lung carcinoma, head and neck squamous cell carcinoma, urinary bladder cancer, and renal cell cancer). Potential risks exist for tiragolumab based on the mechanism of action, known effects of checkpoint inhibitors, and nonclinical data, such as autoimmune inflammation (also described as immune-mediated adverse events) and ADCC-mediated lymphopenia. TLS is an additional potential risk when tiragolumab is administered in patients with hematological malignancy.

Atezolizumab has been associated with risks such as IRRs, immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial*

disorders, nephritis, and myositis. *In addition,* immune-mediated reactions may involve any organ system and lead to HLH.

Based on nonclinical and clinical single-agent data, there are potential overlapping toxicities for the combination of mosunetuzumab with tiragolumab and atezolizumab. The potential exists that mosunetuzumab, tiragolumab, and atezolizumab exacerbate each other's respective immune-mediated toxicities associated with their use as single agents. Specific areas of potential overlapping or exacerbated toxicities due to concomitant use, based on the potential or identified risks of each agent, include CRS and IRRs, HLH, neurologic adverse events, tumor flare, TLS, and elevated liver enzymes and hepatic events.

See Appendix 6 for information on anticipated risks for mosunetuzumab, tiragolumab, and atezolizumab and risk mitigation measures, including guidelines for managing adverse events associated with mosunetuzumab, tiragolumab, and atezolizumab.

More detailed information about the known and expected benefits and risks and adverse drug reactions of mosunetuzumab, tiragolumab, and atezolizumab considered expected for regulatory reporting purposes may be found in the respective Investigator's Brochures.

Taking into account the relatively poor prognosis of patients with R/R hematologic malignancies that have failed standard therapies, the efficacy data of mosunetuzumab in patients with R/R NHL, the safety profile for mosunetuzumab, tiragolumab, and atezolizumab, and the risk mitigation measures for the study, the benefit–risk ratio is expected to be acceptable for mosunetuzumab in combination with tiragolumab and mosunetuzumab in combination with tiragolumab and atezolizumab in the setting of R/R NHL.

2.3.1 COVID-19 Benefit–Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities including those with FL and DLBCL may be a more vulnerable patient population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of SARS-CoV-2 infection, and at this time, there is insufficient evidence for causal association between mosunetuzumab, atezolizumab, tiragolumab, or tocilizumab and an increased risk of severe outcomes from SARS-CoV-2 infection. Tocilizumab has been approved or received Emergency Use Authorization for the treatment of severe COVID-19 in several countries.

A possible consequence of inhibiting immune checkpoints may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-L1/PD-1 blockade

appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13; Frebel et al. 2012; Wykes and Lewin 2018; Schorer et al. 2020). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with dysregulated immune response involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). Patients with known active infection will be excluded from the study (Section 5.2) and guidance on the risk and management of infections for study participants is provided in Sections A6–1.1.4 and A6–2.3.7. There may be overlapping clinical features of cancer immunotherapy–related CRS and severe COVID-19 driven by hyperinflammatory response. Mosunetuzumab has the identified risk of CRS, although it is not known if there may be potential for an increased risk of an enhanced inflammatory response if a participant develops acute SARS-CoV-2 infection while receiving mosunetuzumab. Interstitial pneumonia may be associated with the study drugs used in this trial or SARS-CoV-2 infection. Investigators should use their clinical judgment when evaluating and managing patients with suspected signs and symptoms. *Study treatment should not be administered in the presence of active SARS-CoV-2 infection. If a participant is infected with SARS-CoV-2 while in the study, the infection should be clinically resolved before resumption of study treatment (see Sections A6–1.1.4 and A6–2.3.7 for further guidance).* See Section 6.8.4.1 for benefit–risk considerations around the administration of COVID-19 vaccines for candidates or participants of this study, and guidance on COVID-19 vaccine administration and timing.

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of mosunetuzumab in combination with tiragolumab, with or without atezolizumab, in participants with R/R DLBCL or FL who have received at least two previous lines of systemic therapy.

Specific objectives and corresponding endpoints for the study are outlined in Table 4.

In this protocol, "study treatment" refers to the combination of treatments assigned to participants as part of this study (i.e., either mosunetuzumab in combination with tiragolumab or mosunetuzumab in combination with tiragolumab and atezolizumab).

Table 4 Objectives and Corresponding Endpoints

Phase Ib–Specific Objectives	
Primary Objectives	
Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety of mosunetuzumab SC in combination with tiragolumab IV, including evaluation of the tolerability of the dosing schedule and dose, and characterization of DLTs in Cohort A and Cohort B • To evaluate the safety of mosunetuzumab SC with tiragolumab IV and atezolizumab IV, including evaluation of the tolerability of the dosing schedule and dose, and characterization of DLTs in Cohort E	• Incidence and severity of adverse events, including DLTs, with severity determined according to NCI CTCAE v5.0; for CRS, severity determined according to ASTCT CRS consensus grading criteria (Appendix 9)
Secondary Objectives	
Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the preliminary efficacy of mosunetuzumab SC in combination with tiragolumab IV in Cohorts A and B • To evaluate the preliminary efficacy of mosunetuzumab SC with tiragolumab IV and atezolizumab IV in Cohort E	• Best ORR (CR or PR at any time) in the study as determined by the investigator using Lugano 2014 criteria (Appendix 10) • Best CR rate, defined as the proportion of participants whose best overall response is a complete response during the study, as determined by the investigator using Lugano 2014 criteria (Appendix 10) • DOR, defined as the time from the first occurrence of a documented objective response (CR or PR) to disease progression or relapse, as determined by the investigator using Lugano 2014 criteria (Appendix 10), or death from any cause, whichever occurs first

Table 4 Objectives and Corresponding Endpoints (cont.)

Phase II–Specific Objectives	
Primary Objectives	
Efficacy Objectives	**Corresponding Endpoint**
• To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV in participants with R/R FL (Cohort C) • To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV in participants with R/R DLBCL (Cohort D) • To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV in participants with FL (Cohort F)	• Best ORR, defined as the proportion of participants whose best overall response is a PR or a CR during the study, as determined by the investigator using Lugano 2014 criteria (Appendix 10)
Secondary Objectives	
Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV in participants with R/R FL (Cohort C) • To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV in participants with R/R DLBCL (Cohort D) • To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV in participants with R/R FL (Cohort F)	• Best CR rate in the study, as determined by the investigator using Lugano 2014 criteria (Appendix 10) • DOR, defined as the time from the first occurrence of a documented objective response (CR or PR) to disease progression or relapse, as determined by the investigator using Lugano 2014 criteria (Appendix 10), or death from any cause, whichever occurs first • PFS, defined as the time from the first study treatment to the first occurrence of disease progression or relapse, as determined by the investigator using Lugano 2014 criteria (Appendix 10), or death from any cause, whichever occurs first • EFS, defined as the time from the first study treatment to the first occurrence of disease progression or relapse, as determined by the investigator using Lugano 2014 criteria (Appendix 10), initiation of NALT, or death from any cause, whichever occurs first. • OS, defined as the time from the first study treatment to death from any cause

Table 4 Objectives and Corresponding Endpoints (cont.)

Phase II–Specific Objectives (cont.)	
Secondary Objectives (cont.)	
Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety of mosunetuzumab in combination with tiragolumab in participants with R/R FL (Cohort C) • To evaluate the safety of mosunetuzumab in combination with tiragolumab in participants with R/R DLBCL (Cohort D) • To evaluate the safety of mosunetuzumab with tiragolumab and atezolizumab in participants with R/R FL (Cohort F)	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v5.0; for CRS, severity determined according to the ASTCT CRS Consensus Grading criteria (Appendix 9)
Objectives for Both Phase Ib and Phase II	
Secondary Objectives	
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the PK profile of mosunetuzumab SC in combination with tiragolumab IV (Cohort A, Cohort B, Cohort C, and Cohort D) • To characterize the PK profile of mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV (Cohort E and Cohort F)	• C_{max} • C_{min} • Total exposure (AUC), CL, and volume of distribution, as estimated by population-PK modeling, as appropriate, and supported by data
Exploratory Objectives	
Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV in participants with R/R FL (Cohort C) • To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV in participants with R/R DLBCL (Cohort D) • To evaluate the efficacy of mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV in participants with R/R FL (Cohort F)	• Best ORR, defined as the proportion of participants whose best overall response is a PR or a CR during the study, as determined by automated response using Lugano 2014 criteria (aLugano)
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the pharmacokinetics of tiragolumab IV when administered in combination with mosunetuzumab SC (Cohort A, Cohort B, Cohort C, and Cohort D) and when in combination with mosunetuzumab SC and atezolizumab IV (Cohort E and Cohort F)	• C_{max} • C_{min} • Total exposure (AUC), CL, and volume of distribution, as estimated by population-PK modeling, as appropriate, and supported by data

Table 4 Objectives and Corresponding Endpoints (cont.)

Objectives for Both Phase Ib and Phase II (cont.)	
Secondary Objectives (cont.)	
Pharmacokinetic Objectives (cont.)	**Corresponding Endpoints (cont.)**
• To characterize the pharmacokinetics of atezolizumab IV when administered in combination with mosunetuzumab SC and tiragolumab IV (Cohort E and Cohort F)	• C_{max} • C_{min} • Total exposure (AUC), CL, and volume of distribution, as estimated by population-PK modeling, as appropriate, and supported by data
• To assess potential PK interactions between mosunetuzumab SC and tiragolumab IV • To assess potential PK interactions between mosunetuzumab SC, tiragolumab IV and atezolizumab IV	• PK parameters for mosunetuzumab given in combination with tiragolumab compared with mosunetuzumab given alone based on historical data • PK parameters for tiragolumab given in combination with mosunetuzumab compared with tiragolumab given alone based on historical data • PK parameters for mosunetuzumab in combination with tiragolumab and atezolizumab compared with mosunetuzumab given alone based on historical data • PK parameters for tiragolumab given in combination with mosunetuzumab and atezolizumab compared with tiragolumab given alone based on historical data • PK parameters for atezolizumab given in combination with mosunetuzumab and tiragolumab compared with atezolizumab given alone based on historical data
• To evaluate potential relationships between drug exposure and the efficacy, biomarkers, and safety	• Relationship between PK and safety, biomarkers, or efficacy endpoints, as appropriate

Table 4 Objectives and Corresponding Endpoints (cont.)

Objectives for Both Phase Ib and Phase II (cont.)	
Secondary Objectives (cont.)	
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• To identify biomarkers that are predictive of response to mosunetuzumab SC in combination with only tiragolumab IV (Cohorts A–D), and in combination with tiragolumab IV and atezolizumab IV (Cohorts E and F; i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to mosunetuzumab plus tiragolumab (with or without atezolizumab), are associated with susceptibility to developing adverse events, can provide evidence of mosunetuzumab plus tiragolumab (with or without atezolizumab) activity, or can increase the knowledge and understanding of disease biology • To make a preliminary assessment of response following mosunetuzumab SC in combination with only tiragolumab IV (Cohorts A–D), and in combination with tiragolumab IV and atezolizumab IV (Cohorts E and F) in different clinical and biologic prognostic subgroups of NHL	• Association between prognostic subtypes, exploratory biomarkers, and safety and efficacy endpoints
Exploratory Imaging Objectives	**Corresponding Endpoints**
• To evaluate features generated by deep learning algorithms applied to PET/CT images in participants with R/R FL treated with mosunetuzumab SC in combination with tiragolumab IV, including automated total metabolic tumor volume (aTMTV; Jemaa et al. 2020) and aLugano • To evaluate features generated by deep learning algorithms applied to PET/CT images in participants with R/R DLBCL treated with mosunetuzumab SC in combination with tiragolumab IV	• Concordance of aLugano and response by Lugano 2014 criteria as assessed by Sponsor's radiologist • Concordance of efficacy endpoints using aLugano and efficacy endpoints using response by Lugano 2014 criteria as assessed by Sponsor's radiologist • Concordance of aTMTV and TMTV assessed by Sponsor's radiologist • Relationship between aTMTV and other quantitative indicies such as efficacy, safety, and biomarker endpoints

Table 4 Objectives and Corresponding Endpoints (cont.)

Objectives for Both Phase Ib and Phase II (cont.)	
Secondary Objectives (cont.)	
Exploratory Imaging Objectives (cont.)	**Corresponding Endpoints (cont.)**
• To evaluate features generated by deep learning algorithms applied to PET/CT images in participants with R/R NHL treated with mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV	

ASTCT = American Society for Transplantation and Cellular Therapy; aTMTV = automated total metabolic tumor volume; AUC = area under the concentration–time curve; C_{max} = maximum concentration observed; C_{min} = minimum concentration observed; CR = complete response; CRS = cytokine release syndrome; CT = computed tomography; DLT = dose-limiting toxicity; DLBCL = diffuse large B cell lymphoma; DOR = duration of response; FL = follicular lymphoma; NALT = new anti-lymphoma treatment; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; PET = positron emission tomography; PR = partial response; R/R = relapsed or refractory; TMTV = total metabolic tumor volume.

4. STUDY DESIGN

4.1 STUDY DESIGN OVERVIEW

This is a Phase Ib/II, open-label, two-arm, multicenter study designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of mosunetuzumab SC in combination with tiragolumab IV with or without atezolizumab IV in participants with R/R B-cell NHL, specifically participants with DLBCL, HGBL, trFL, or FL (Grades 1–3b) who have received at least two prior lines of systemic therapy.

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities and a sample collection schedule are provided in Section 1.3 (see Table 1 and Table 2).

Participants will receive 8 cycles of study treatment, including all cycles (C) in which at least one study drug is administered. Participants who achieve PR or SD at the time of primary response assessment (PRA) will continue treatment for a total of 17 cycles in the absence of disease progression.

- **Arm 1: mosunetuzumab SC in combination with tiragolumab IV**—Safety Run-In Cohort A (initial; see Figure 2) and Cohort B (alternate; see Figure 3) will enroll approximately 6 participants with R/R DLBCL, HGBL, trFL, or R/R FL (Grade 1–3b) in each cohort. Following Internal Monitoring Committee (IMC) recommendations on dosing, Expansion Cohort C will enroll approximately 40 participants with R/R FL (Grades 1–3a) and Expansion Cohort D will enroll approximately 40 participants with R/R DLBCL, HGBL, trFL, or R/R FL (Grade 3b).

- **Arm 2: mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV**—Safety Run-In Cohort E (see Figure 4) will enroll approximately 6 participants with R/R DLBCL, HGBL, trFL, or R/R FL (Grade1–3b). Following IMC recommendations on dosing, Expansion Cohort F will enroll approximately 20 participants with R/R FL (Grades 1–3a).

Overall, approximately 6–118 participants will be enrolled in this study at approximately 30 investigative sites globally.

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per individual) at the investigator's discretion (see Section 5.4). For potential participants who are re-screened, all eligibility criteria must be re-evaluated and screening assessments should be repeated as applicable to meet the eligibility criteria outlined in Section 5. The investigator will maintain a record of reasons for screen failure (see Section 8).

All participants will be closely monitored for adverse events throughout the study and for at least 90 days after the final dose of study treatment (see Section 8.3.1). Adverse events will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0), with CRS graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) 2019 CRS Consensus Grading (Lee et al. 2019, Appendix 9). An IMC will be established to monitor patient safety during the study, make recommendations regarding the Safety Run-In dose regimen and overall study conduct on the basis of trial safety data to ensure participant safety while receiving study treatment (Section 4.6).

Participants will be assessed for tumor response by positron emission tomography (PET)/computed tomography (CT) and CT at the interim response assessment (IRA; Cycle 4, Days 15–21) and PRA (Cycle 8, Days 15–21) and at regular intervals during the study treatment and follow-up periods (see Sections 1.3 and 8.1.1 for details). Tumor response will be assessed using the 2014 Lugano Response Criteria (Cheson et al. 2014; see Appendix 10). To characterize the pharmacokinetic (PK) profile and immune response towards study treatment, blood samples will be taken at various timepoints before and after dosing (Table 2 and Sections 8.4, 8.5, 8.7, and 8.8).

Consenting participants in Expansion Cohorts C, D, or F may undergo optional paired tumor biopsies at baseline and between C1 Day (D) 15–C2D1 or C2D15–C3D1 (dependent on the regimen selected from the Safety Run-In Cohorts). Participants may also undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator).

4.1.1 Phase Ib: Safety Run-In Cohorts

The purpose of the Phase Ib Safety Run-In Cohorts is to determine the mosunetuzumab SC step-up dosing schedule and regimen for use in combination with tiragolumab IV with or without atezolizumab IV in patients with R/R NHL.

In order to assess for any severe and unexpected acute drug or injection or infusion-related toxicities, enrollment into the Safety Run-In Cohorts A, B, and E will be staggered. There must be at least 72 hours between each C1D1 dose for the first 3 participants in each cohort. There must be at least 24 hours between each C1D1 dose for subsequent participants in the same cohort. The Sponsor must receive confirmation on the status of the prior participant before the next participant receives study treatment.

Additionally, all participants in the Safety Run-In Cohorts will be hospitalized for 72 hours (based on the end of the last drug administered) after receiving a combination dose for the first time that has not been previously evaluated:

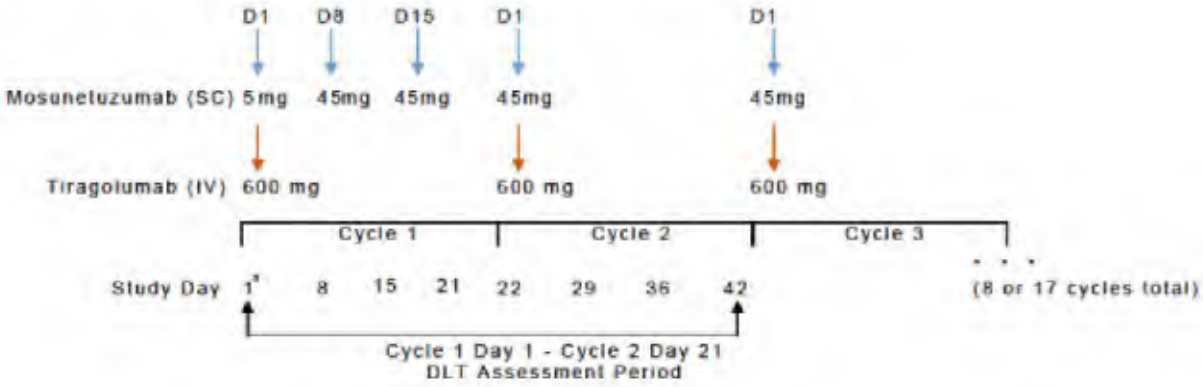
- Participants in Cohort A will be hospitalized for 72 hours (based on the end of the last drug administered) on **C1D1**.
- Participants in Cohort B and Cohort E will be hospitalized for 72 hours (based on the end of the last drug administered) on **C2D1**.

If a participant experiences a CRS Grade ≥2 following single-agent mosunetuzumab or combination administrations, hospitalization at subsequent administration(s) will be required. The investigator should actively assess the need for hospitalization based on the participant's medical factors such as frailty, risk factors for CRS (see Section A6-1.1.1) and prior CRS events, as well as social factors including availability of caregivers at home and distance to the trial sites. All adverse events, including DLTs (Section 4.1.1.3), will be reported according to instructions in Appendix 3 and graded according to NCI CTCAE v5.0 unless otherwise indicated. CRS events will be graded according to the ASTCT CRS Consensus Grading criteria (Appendix 9).

4.1.1.1 Mosunetuzumab SC in Combination with Tiragolumab IV (Arm 1, Cohorts A and B)

Cohort A (Figure 2) will be initiated at the recommended Phase II mosunetuzumab SC step-up dose and schedule of 5 mg on C1D1, 45 mg on C1D8, and 45 mg on C1D15, as determined by the mosunetuzumab Phase I/II Study GO29781 (study currently ongoing). See Section 4.3.1 for background information on the mosunetuzumab SC dose and schedule. Tiragolumab IV will be administered at 600 mg Q3W on D1 of each cycle, starting in C1. See Section 4.3.2 for background information on the tiragolumab dose and schedule.

Figure 2 Cohort A: Initial Dose Regimen and Schedule



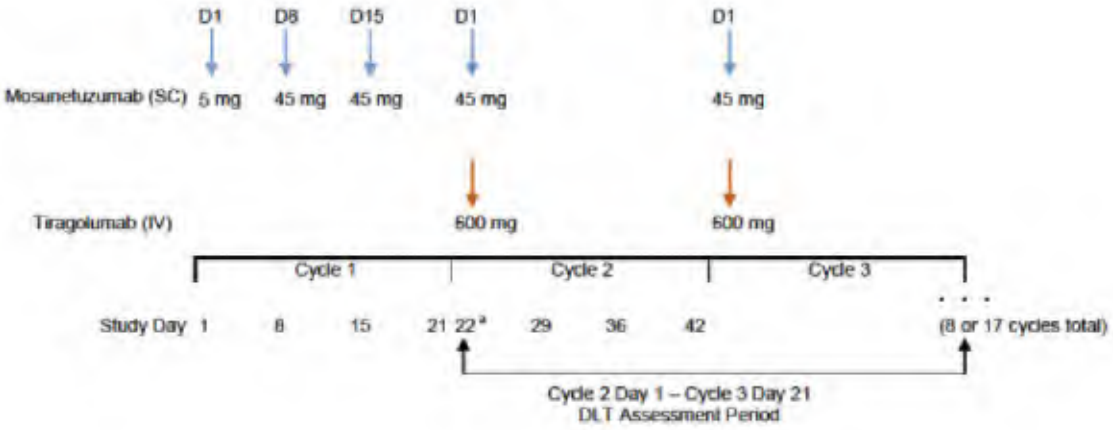
D = day; DLT = dose limiting toxicity.

[a] Participants to be hospitalized for 72 hours following the end of the last study drug administration.

If no more than 1 out of 6 DLT-evaluable participants experiences a DLT, the Expansion Cohorts of Arm 1 (Section 4.1.2) may be opened for enrollment. Tiragolumab administration in these cohorts will be based on the schedule in Cohort A (i.e., it will start on C1D1).

However, if 2 or more participants experience DLT(s) during the Cohort A DLT Assessment Period, or if the totality of data supports a different dose regimen, Cohort B (with an alternate dose regimen) may be initiated per IMC recommendation (Figure 3). In Cohort B, mosunetuzumab SC is administered at the same dose and schedule as in Cohort A, but the first dose of tiragolumab will be administered on C2D1.

Figure 3 Cohort B: Alternate Dose Regimen



D = day; DLT = dose limiting toxicity.

[a] Participants to be hospitalized for 72 hours following the end of the last study drug administration.

If no more than 1 out of 6 DLT-evaluable participants experiences a DLT in Cohort B, the Expansion Cohorts of Arm 1 (Section 4.1.2) may be opened for enrollment. Tiragolumab administration in these cohorts will be based on the schedule in Cohort B (i.e., it will start on C2D1).

However, if 2 or more participants experience a DLT in Cohort B, or the totality of data supports a lower dose, an additional dose de-escalation cohort of approximately 6 participants each may be initiated per IMC recommendation to assess a lower dose level of mosunetuzumab or tiragolumab in combination with the same dosing schedule and hospitalization requirement as in Cohort B (i.e., mosunetuzumab step-up dosing in Cycle 1 and start of tiragolumab administration in Cycle 2). The safety data for this lower dose group will be evaluated after 6 participants in that cohort have completed 21 days of study treatment (Days 1–21 of Cycle 2).

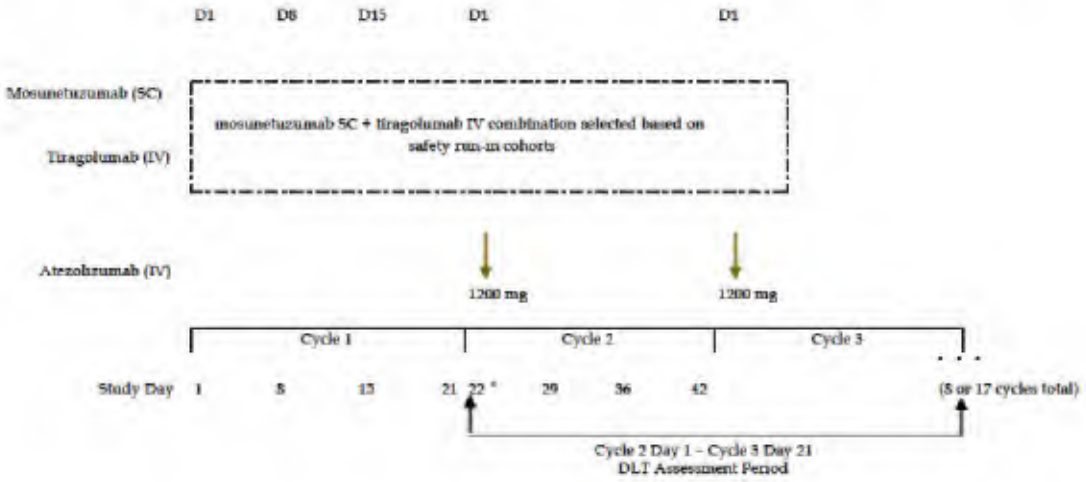
If no more than 1 out of 6 DLT-evaluable participants experience a DLT in this dose de-escalation cohort, the Expansion Cohorts of Arm 1 (Section 4.1.2) may be opened for enrollment, with the start of tiragolumab administration on C2D1 and the doses evaluated in the dose de-escalation cohort.

If additional dosing schedules or dose de-escalations are to be evaluated, a protocol amendment will be submitted with rationale for the proposed change.

4.1.1.2 Mosunetuzumab SC in Combination with Tiragolumab IV with Atezolizumab IV (Cohort E)

Cohort E may be opened for enrollment based on safety and efficacy data analyzed at the interim analysis after 20 participants have been enrolled in Expansion Cohort C and upon recommendation of the IMC (Section 9.5.1 and 9.5.2). Cohort E will assess the safety of mosunetuzumab SC in combination with tiragolumab IV and atezolizumab IV in participants with R/R DLBCL, HGBL, trFL, or R/R FL (Grades 1–3b; Figure 4).
See Section 4.3.3 for the rationale of the atezolizumab dose and schedule.

Figure 4 Cohort E: Safety Run-In for Mosunetuzumab SC in Combination with Tiragolumab IV with Atezolizumab IV



D = day; DLT = dose limiting toxicity.

[a] Participants to be hospitalized for 72 hours following the end of the last study drug administration.

If no more than 1 out of 6 DLT-evaluable participants experience a DLT in Cohort E, the expansion cohort of Arm 2 (Section 4.1.2) may be opened for enrollment.

If additional dosing schedules or dose de-escalations are to be evaluated, a protocol amendment will be submitted with rationale for the proposed change.

4.1.1.3 Definition of Dose Limiting Toxicity

In the Safety Run-In Cohorts A, B, and E, a DLT is defined as any one of the following events occurring during the DLT Assessment Period:

- Any Grade ≥3 hematologic adverse event in the absence of another clearly identifiable cause, with the following exceptions:

- Grade 3 or 4 neutropenia that is not accompanied by temperature elevation (as a single oral temperature of ≥38.3°C [101°F] or an oral temperature of ≥38.0°C [100.4°F] sustained for ≥1 hour) and improves to Grade ≤2 (or to ≥80% of the baseline value, whichever is lower) without a delay of the next scheduled cycle of study treatment exceeding 7 days
- Grade 3 or 4 thrombocytopenia that improves to Grade ≤2 (or to ≥80% of the baseline value, whichever is lower) before D1 of the next scheduled cycle of study treatment without platelet transfusion and is not associated with bleeding that is considered clinically significant by the investigator
- Grade 3 or 4 anemia that does not require an emergent transfusion
- Decreases in B cells, lymphopenia, and/or leukopenia due to decreases in B cells will not be considered DLTs as they are expected PD outcomes of mosunetuzumab, tiragolumab, and atezolizumab treatment.

- Any Grade ≥3 non-hematologic adverse event not considered by the investigator to be attributable to another clearly identifiable cause, with the following exceptions:
  - Grade 3 diarrhea, nausea, or vomiting that can be managed with standard-of-care therapy and resolution to Grade ≤2 within 72 hours
  - Grade 3 laboratory abnormality that is asymptomatic and deemed by the investigator not to be clinically significant
  - Grade 3 fatigue lasting ≤3 days
  - Grade 3 (NCI CTCAE v5.0) individual signs and symptoms of CRS [1] after mosunetuzumab injection (Appendix 6, Section A6–1.1.1) that occurs in the context of Grade ≤2 CRS (as defined by the ASTCT CRS Consensus Grading criteria; Appendix 9) and lasts <3 days will not be considered a DLT.
  - Grade 3 elevation in ALT or AST, provided there are no clinical signs or symptoms of hepatic injury and it resolves to Grade ≤2 within 3 days
  - Grade 3 infusion-related reaction that can be successfully managed and for which the signs and symptoms resolve to Grade ≤1 within 5 days.
  - The following additional exceptions apply for Cohort E:

    Grade 3 rash that resolves to Grade ≤2 in ≤7 days with therapy equivalent to prednisone 10 mg/day or less

    Grade 3 arthralgia that can be adequately managed with supportive care or that resolves to Grade ≤2 within 7 days

[1] Although CRS will be graded according to the ASTCT CRS consensus grading criteria (Appendix 9), for dose modification decisions, DLTs related to CRS will be defined based on individual signs and symptoms and laboratory data (Appendix 3) according to NCI CTCAE v5.0.

Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine therapy that would not necessitate initiation of systemic corticosteroids (with the exception of replacement steroids for adrenal insufficiency)

- Any event involving an increase in hepatic transaminase $>3\times$ baseline in combination with either an increase in direct bilirubin $>2\times$ upper limit of normal (ULN) or clinical jaundice, without any findings of cholestasis or signs of hepatic dysfunction and in the absence of other contributory factors (e.g., worsening of metastatic disease or concomitant exposure to known hepatotoxic agent or of a documented infectious etiology) is suggestive of potential drug-induced liver injury (according to Hy's Law) and will be considered a DLT unless the following criteria are met:
  - Any AST or ALT $>3\times$ the ULN and total bilirubin $>2\times$ ULN where no individual laboratory value exceeds Grade 3 and lasts <3 days will not be considered a DLT.

4.1.1.4 Dose Limiting Toxicity Period

In Cohorts A and B, the DLT Assessment Period will be based on the timing of the first administration of mosunetuzumab in combination with tiragolumab as follows:

- **Cohort A:** C1D1 through C2D21
- **Cohort B:** C2D1 through C3D21

For Cohort E, DLTs will be assessed after the first administration of mosunetuzumab in combination with tiragolumab and atezolizumab:

- **Cohort E:** C2D1 through C3D21

During each Safety Run-In Cohort, an IMC safety review of data will take place after 6 participants complete the DLT assessment period, or if 2 participants develop a DLT (see Section 4.1.1.5 for DLT Evaluable Criteria).

4.1.1.5 Definition of "DLT Evaluable"

Determination of whether a participant is evaluable for DLT assessment will be made in accordance with the following rules:

- Participants who receive study treatment with mosunetuzumab SC and tiragolumab IV (Cohort A and Cohort B) or mosunetuzumab SC and tiragolumab IV and atezolizumab IV (Cohort E) and remain in the study through the DLT assessment window will be considered DLT evaluable.
- Participants who develop a DLT during the DLT Assessment Period will be considered DLT evaluable.
- Participants who discontinue from study treatment prior to completing the DLT assessment window for reasons other than a DLT will be deemed non-evaluable for DLT evaluation and will be replaced with an additional participant.

- For participants in Cohort A who have dose delays of mosunetuzumab exceeding 7 days following a scheduled dose during the DLT Assessment Period (see Appendix 6, Section A6–2.2) for a non-DLT adverse event may be deemed DLT-unevaluable and may be replaced at the discretion of the Medical Monitor.

4.1.2 Phase II: Expansion Phase

The purpose of the Phase II Expansion Cohorts C, D, and F is to further assess the safety and efficacy of mosunetuzumab SC and tiragolumab IV with or without atezolizumab IV at the dose and schedule determined by the Safety Run-In. The dose and schedule of study treatment to be assessed in the Expansion Cohorts will be selected based on the Safety Run-In Cohorts and review of cumulative safety data by the IMC. Patients with R/R FL or R/R DLBCL will be enrolled during the expansion phase and treated as described below:

- Cohort C (mosunetuzumab SC and tiragolumab IV): R/R FL (Grade 1–3a); approximately 40 participants
- Cohort D (mosunetuzumab SC and tiragolumab IV): R/R DLBCL, HGBL, trFL, or R/R FL (Grade 3b); approximately 40 participants
- Cohort F (mosunetuzumab SC, tiragolumab IV, and atezolizumab IV): R/R FL grade (Grade 1–3a); approximately 20 participants

The Sponsor may limit the number of patients with particular NHL subtypes enrolled in each cohort.

4.1.2.1 IMC Safety Review in the Expansion Phase

For each study arm, an additional IMC safety review of cumulative data will take place after 6 participants have been enrolled in any of the corresponding expansion cohorts and reached C2D21 or discontinued treatment. If any of the following criteria are met by the time of the IMC safety review, then accrual to the expansion cohorts in that arm may be paused, and the IMC may recommend that study treatment and/or further enrollment in the cohort be halted in order to perform a comprehensive review of the safety data:

- ≥ 10% treatment-related fatal adverse events (excluding disease progression)
- > 50% Grade 3 or higher serious adverse events related to study treatment

4.1.3 Mosunetuzumab SC, Tiragolumab IV, and Atezolizumab IV Re-Treatment

Participants who achieve a complete response during initial treatment and experience disease relapse after completion of study treatment will be eligible for re-treatment with mosunetuzumab and tiragolumab (Cohort A, Cohort B, Cohort C, and Cohort D) or mosunetuzumab, tiragolumab, and atezolizumab (Cohort E and Cohort F) as described below. The study re-treatment dose and schedule will be one that has been previously

demonstrated to be safe in the Safety Run-In Cohorts, provided the following criteria are met:

- Pertinent eligibility criteria (see Sections 5.1 and 5.2) are met at the time treatment is re-initiated with the following exceptions:
  - Previous treatment with mosunetuzumab, tiragolumab, or atezolizumab is allowed.
  - Serology tests to demonstrate human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) status do not need to be repeated unless clinically indicated. Epstein-Barr virus (EBV) and cytomegalovirus quantitative PCR must be repeated.
  - Manageable and reversible immune-related adverse events of Grades 1–3 with initial study treatment are allowed and do not constitute an exclusionary history of autoimmune disease.
  - Endocrinopathy of any grade managed with replacement therapy or asymptomatic elevation of serum amylase or lipase of any grade is allowed.
- Participants must not have experienced Grade 4 non-hematologic adverse events that were not considered by the investigator to be attributable to another clearly identifiable cause during initial study treatment, with TLS and CRS as possible exceptions (see Section A6–2.2).
- Participants who experienced Grade 2 or 3 adverse events that were not considered by the investigator to be attributable to another clearly identifiable cause during initial treatment must have resolved to ≤Grade 1. Laboratory values must meet the requirements specified in the inclusion criteria with the respective exceptions.
- No intervening systemic anti-cancer therapy was administered between the completion of initial study treatment and re-initiation of study treatment.
- Written informed consent is provided to acknowledge deferring any standard treatment options that may exist in favor of reinitiating study treatment and to undergo a biopsy of recurrent or progressing tumor if clinically feasible.

For participants proceeding to re-treatment following disease progression, a repeat tumor biopsy is strongly suggested if a lesion is amenable for biopsy at disease progression, in order to assess the status of the tumor (e.g., CD20, TIGIT, and PD-1 expression status), and changes or status of the immune microenvironment.

The dose and schedule of study treatment to be administered for participants receiving re-treatment will be determined by the Medical Monitor and will be a previously tested dose and schedule for which all participants of the respective Safety Run-In Cohort cleared the DLT observation period. The hospitalization requirements for the respective dose and schedule will apply based on the recommendation of the IMC (Section 4.5). Participants may require hospitalization following the first re-treatment administration.

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

This study will enroll patients with a history of hematologic malignancy that is expected to express the CD20 antigen, specifically DLBCL and FL. Central confirmation of CD20 expression will not be required during eligibility screening prior to enrollment, but it will be evaluated retrospectively, based on the following rationale:

- CD20 is expressed in a majority of the B-cell–derived malignancies, including NHL.
- Nonclinical studies have demonstrated that mosunetuzumab is broadly active in killing multiple human B lymphoma cell lines with a broad range of CD20 expression levels, including cell lines with very low levels of CD20 expression that are not efficiently killed by rituximab or obinutuzumab, suggesting that even very low levels of CD20 expression may be sufficient for clinical activity.
- Although a few lymphomas may express relatively low levels of CD20, current information regarding the histologies in the intended study suggest that truly negative tumors (i.e., expressing no detectable CD20) are infrequent (Miyoshi et al. 2012).

4.2.1.1 Relapsed or Refractory Follicular Lymphoma

Despite significant therapeutic progress with the use of immunochemotherapy as first-line treatment, FL remains an incurable disease and most patients will eventually relapse. Relapses are characterized by increasing refractoriness and decreasing DOR to subsequent lines of therapy. Thus, new treatments are needed to improve the outcome for multiply relapsed patients. Treatment options for R/R FL include lenalidomide with rituximab, as well as immunochemotherapy similar to the first-line therapy with rituximab or obinutuzumab (National Comprehensive Cancer Network [NCCN] 2020). In patients with rituximab-refractory indolent NHL, obinutuzumab plus bendamustine followed by obinutuzumab maintenance demonstrated improved PFS and OS compared with bendamustine alone (Sehn et al. 2016; Cheson et al. 2018). The U.S. FDA *initially* granted accelerated approval to *the inhibitors of phosphoinositide 3'–kinase (PI3K)* idelalisib (Zydelig®), duvelisib (Copiktra®), copanlisib (Aliqopa®), and tazemetostat (Tazverik®) as single agents for the treatment of patients with relapsed FL who have received at least two prior systemic therapies. These agents result in partial, but not complete, responses in a majority of patients with R/R FL, and both are associated with a median PFS of less than 1 year in single-arm studies (Dreyling et al. 2017). Furthermore, these agents have been associated with significant toxicities in some patients.

Copanlisib was evaluated in a single-arm, multicenter study (CHRONOS 1) in 104 patients with FL who had relapsed disease following at least two prior treatments (Dreyling et al. 2017). The complete response rate (CR) was 14%. Idelalisib was evaluated in a single-arm, multicenter study (DELTA) in 72 patients with FL who had relapsed disease following at least two prior treatments (Gopal et al. 2014). The CR rate was reported to be 8% and 16.7% respectively (Zydelig USPI; Zydelig EMA

Summary of Product Characteristics [SmPC]). Duvelisib was evaluated in a single-arm, multicenter study (DYNAMO) in 83 patients with FL who had relapsed disease following at least two prior treatments (Flinn et al. 2019; Copiktra EMA SmPC). No CRs were observed. Additional considerations related to the PI3K drug class are highlighted in the PI3K inhibitor class advisory committee meeting of non-FDA experts in April 2022, concerning trends in overall survival (OS) in multiple randomized controlled trials, toxicities of the PI3K inhibitor class, inadequate dose optimization, and trial design considerations regarding the limitations of single-arm trials (FDA Briefing Document 2022). The accelerated approvals for idelalisib in FL and for duvelisib in FL and small lymphocytic lymphoma have since been withdrawn in the United States in Q1 2022 and Q4 2021, respectively. Idelalisib and duvelisib are approved in the European Union and other countries.

Multiply relapsed FL thus remains a disease with high unmet medical need for which improved therapies are needed.

4.2.1.2 Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Up to 40% of patients with DLBCL who are treated in the first-line setting will progress within 3 to 4 years, and more than half of the patients treated with second-line therapies do not achieve a complete remission (Gisselbrecht et al. 2010; Friedberg 2011). Furthermore, since the introduction of the monoclonal anti-CD20 antibody rituximab, it has become more challenging to find effective therapies for the large proportion of patients with R/R DLBCL who have prior exposure to rituximab.

Polatuzumab vedotin, an antibody-drug conjugate targeting CD79b, in combination with bendamustine and rituximab (BR) was granted accelerated approval from U.S. FDA and Conditional Marketing Authorization from EMA for the treatment of R/R DLBCL. In the randomized Phase II part of the Study GO29365, polatuzumab vedontin plus BR (n=40) showed better efficacy than BR alone (n=40) in transplant-ineligible patients with R/R DLBCL marked by CR rate at the end of the treatment (40.0% vs. 17.5%, p=0.026), PFS (median 9.5 months vs. 3.7 months, p<0.001; both assessed by IRC), and OS (median 12.4 months vs. 4.7 months, p=0.002; Sehn et al 2019).

Tafasitamab, a humanized anti-CD19 monoclonal antibody, in combination with lenalidomide, received accelerated approval from U.S. FDA in the treatment of transplant-ineligible patients with R/R DLBCL after at least one line of therapy. Best response rate was 60%, including best CR rate of 43%, with median duration of response of 21.7 months (Salles et al. 2020). While the response rates and the duration of therapy were clinically significant, the study excluded very high-risk population such as primary refractory disease and double-hit lymphoma, and thus, provides limited benefit in the area of highest unmet medical need.

Selinexor recently received an accelerated approval by U.S. FDA in the treatment of DLBCL after at least two lines of prior systemic therapy. In the 127 participant evaluable

population, Grade 3 or 4 thrombocytopenia was observed in 46% of participants. ORR was 29%, including CR rate of 13%. Although this is an oral regimen with significant convenience, the untrivial myelosuppression and the low response rates may limit the actual use of this regimen in this setting.

In addition, two of CD19-directed CAR T cell therapies were approved by U.S. FDA and EMA for use in the third-line or later setting (axicabtagene ciloleucel [Yescarta® United States Prescribing Information; USPI] and tisagenlecleucel [Kymriah® USPI]). Although these therapies have shown efficacy with durable CRs, their use may be limited for the general R/R DLBCL population due to the toxicity profile which requires carefully selected patients and treatment in centers with specially trained staff. In addition, the waiting period associated with CAR T manufacture may be prohibitive in patients with rapidly progressing disease.

Despite above mentioned improvement in the therapeutic approaches in R/R DLBCL, the clinical outcome of patients with this condition, especially those who are not eligible for transplant, is still poor. Of note, tafasitamab and CAR-T products target the same antigen, CD19, raising the concern for potential cross-resistance. Taken together, there remains a significant unmet medical need for patients with transplant-ineligible R/R DLBCL.

4.2.1.3 High Grade B-Cell Lymphomas

High grade B-cell lymphomas (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBL-double hit) and HGBL not otherwise specified (HGBL-NOS) are new separate entities in the 2016 revised WHO classification of lymphoid neoplasms (Swerdlow 2016). These entities lack therapeutic standards in the first line and in the relapsed setting (Novo et al. 2019, NCCN guidelines 2020). For HGBL in the R/R setting, the NCCN guidelines refer to the treatment recommendations for R/R DLBCL. The CD19-directed CAR T cell therapies axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah) have been approved for use in HGBL by the FDA for use in the third-line or later setting, but the same limitations apply to their use as mentioned above. There is a high unmet medical need to develop novel therapeutics for these diseases and they will be eligible for enrollment in the same cohorts as patients with de-novo DLBCL.

4.2.2 Transformed Follicular Lymphoma

Each year around 3% of FLs transform into higher-grade NHL, most commonly DLBCL, leading to almost a third of patients diagnosed with histologic transformation over 10 years (Lossos and Gascoyne 2011). Patients with DLBCL transformed from a previous FL histology are treated with the same standard therapies as high grade lymphomas and will therefore be eligible for enrollment in the same cohorts as patients with de-novo DLBCL.

4.2.2.1 FL Grade 3b

Follicular lymphoma Grade 3 is commonly sub-divided into Grades 3a and 3b based on histological quantification of the diffuse component. Follicular lymphoma Grade 3b has more in common genetically, immunophenotypically, and clinically with DLBCL than with indolent FL, and the coexistence with DLBCL is frequent (Harris and Kluin 2011). Based on clinical behavior similar to aggressive NHL, patients with FL Grade 3b are treated similarly to patients with DLBCL (Wahlin et al. 2012; NCCN 2020). This patient population will therefore be eligible for treatment in the same cohorts as patients with DLBCL but not in the Expansion Cohorts for FL.

4.2.3 Rationale for Biomarker Assessments

Predictive and prognostic biomarkers, including biomarkers associated with disease biology, drug targets, the mechanism of action of the individual components or the synergistic activity of the combinations, may correlate with outcome in participants with R/R DLBCL and FL treated in this study. Tumor biopsies will be obtained at baseline from participants with safely accessible tumors as detailed in Section 8.7 to assess tumor and tumor immune microenvironment profiles using technologies such as immunohistochemistry, gene expression, or mutation profiling to evaluate associations with the drugs, prognostic subtypes, or outcome.

Changes in immune-related biomarkers in blood may provide evidence for biologic activity of the combination of mosunetuzumab and tiragolumab treatment, and for the combination of mosunetuzumab with tiragolumab and atezolizumab. An exploratory objective of this study is to assess potential pharmacodynamic biomarkers (including but not limited to cytokines, T cell activation and proliferation, NK cells, B cells, and other exploratory biomarkers) in blood samples. In addition, potential correlations of these biomarkers with the dose, safety, anti-tumor activity, or resistance to the respective combination therapies will be explored.

Evaluating changes to the tumor and the tumor immune microenvironment is important for understanding potential mechanisms of resistance as well as understanding how the pharmacodynamic effects differ across the two treatment combinations. The targets of mosunetuzumab, tiragolumab, and atezolizumab are expressed on both distinct and overlapping immune cell subsets and on the B-cell tumor itself. In an effort to understand the relationship between expression patterns of these targets on cells in the tumor area, optional, paired biopsies obtained at baseline, on-treatment, or at-progression will be evaluated using single-nucleotide RNAseq in an effort to understand the complex interplay that may be associated with response or resistance.

Additionally, exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by

the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

Participants experiencing disease progression or disease relapse after treatment with mosunetuzumab in combination with tiragolumab or mosunetuzumab with tiragolumab and atezolizumab may be eligible for re-treatment (Section 4.1.3). Given that loss of CD20 expression after mosunetuzumab treatment is a potential mechanism of resistance to anti-CD20 therapy, potentially similar to antigen-loss escape resistance mechanisms observed with other T cell bispecific therapies, a repeat biopsy from a safely accessible site should be obtained which may be used to confirm CD20 expression, TIGIT expression, changes in PD-1, and to assess tumor immune status prior to re-treatment (Topp et al. 2011).

In addition to the exploratory objectives listed above, specimens (if consent is given) stored in the Research Biosample Repository (RBR) will also be used for the following:

- To evaluate the association of biomarkers with efficacy and/or adverse events associated with mosunetuzumab in combination with tiragolumab or mosunetuzumab with tiragolumab and atezolizumab
- To increase the knowledge and understanding of disease biology and/or to develop biomarker or diagnostic assays and to establish the performance characteristics of these assays

On the basis of continuous analysis of the data in this study and other cancer immunotherapy nonclinical and clinical studies, or on the basis of new data from literature, collection of samples or biomarker analyses with exploratory purposes may be stopped at any time.

4.2.4 Rationale for Pharmacokinetic Sampling Schedule

The PK sampling schedule that follows the mosunetuzumab administration is designed to capture data at a sufficient number of timepoints to inform the concentration-time curve and enable characterization of the key PK parameters (including but not limited to C_{max}, C_{min}, and area under the concentration–time curve [AUC]) for mosunetuzumab in combination with tiragolumab or in combination with tiragolumab and atezolizumab. The PK sampling schedule for tiragolumab and atezolizumab is designed to characterize key PK parameters of each study drug respectively when administered in combination with mosunetuzumab. Additionally, predose serum rituximab or obinutuzumab PK samples are required to characterize any potential interactions between rituximab or obinutuzumab PK and the clinical effects of mosunetuzumab. These data will be used to understand the relationship of PK exposure to dose and support characterization of dose/exposure–response relationships in the combination setting. In addition, these data will be used to explore and characterize the potential PK interactions between mosunetuzumab and

tiragolumab and among mosunetuzumab, tiragolumab, and atezolizumab given in combination.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

4.3.1 Rationale for Subcutaneous Step-Up Dosing of Mosunetuzumab

In this study, mosunetuzumab will be administered subcutaneously in a 21-day cycle with a step-up dosing schedule in C1. Overall, the rationale of assessing SC step-up dosing schedule for mosunetuzumab is to potentially minimize cytokine-driven toxicities upon initial mosunetuzumab dosing and thus maximize the benefit–risk profiles. Firstly, the concept of Cycle 1 step-up dosing was proven to greatly mitigate CRS risk for mosunetuzumab IV on the basis of previous clinical experience in Study GO29781 (Bartlett 2019). Further, mosunetuzumab SC is expected to further mitigate acute toxicity of CRS as a result of favorable PK profiles with reduced C_{max} and similar exposure when compared directly with an IV dose at an equivalent dose and regimen. The current PK data (1.6–20 mg Q3W; n=23) indicate that mosunetuzumab has a favorable SC PK profile with high bioavailability (>95%) and a slow absorption rate (absorption rate constant approximately 0.134 day–1; T_{max} approximately 3–8 days).

The SC administration of mosunetuzumab is an attractive option for CRS mitigation and participant convenience. Subcutaneous administration of mosunetuzumab is currently being tested in Study GO29781 and has shown a favorable safety profile. Mosunetuzumab SC has been evaluated in a fixed-dose escalation with fixed doses between 1.6–20 mg (Group D of Study GO29781). One DLT (Grade 4 neutropenia; resolved) was observed at the dose of 1.6 mg. No adverse events led to treatment discontinuation. Common (>20%) adverse events related to mosunetuzumab SC included CRS (n=13; 28%), injection-site reaction (n=27; 59%; 52% Grade 1 and 7% Grade 2), and neutropenia (n=14; 30%; all Grade 1). Most CRS events, graded by ASTCT Consensus Grading Criteria, occurred during Cycle 1 (93%), and all of them were Grade 1 (n=9; 20%) or Grade 2 (n=4; 9%; Lee et al. 2019). In contrast to the Q3W fixed-dosing IV cohort, the safety profile of mosunetuzumab SC was favorable. Notably, the frequency of Grade 2 CRS events was lower with mosunetuzumab SC versus the IV fixed-dosing group despite 7-fold higher dose levels. No neurological symptoms (defined as any Preferred Terms in the Nervous System Disorders and Psychiatric Disorders System Organ Class) associated with CRS were reported. Refer to the Mosunetuzumab Investigator's Brochure for more details on the safety data.

To further reduce the rate and severity of CRS events, mosunetuzumab SC step-up dosing regimen is being evaluated in Study GO29781 Group F. The initial Cohort F1 evaluated 5 mg on C1D1, 15 mg on C1D8, and 45 mg on C1D15, followed by 45 mg on Day 1 of subsequent cycles (Q3W; dosing schedule referred to as "5/15/45 mg"). Compared with the highest cleared mosunetuzumab IV step-up dose of C1D1 at 1 mg, C1D8 at 2 mg, C1D15, and C2D1 at 60 mg, followed by Day 1 of subsequent cycles

(Q3W) at 30 mg (dosing schedule referred to as "1/2/60/30 mg"), the selected mosunetuzumab SC doses are projected to achieve comparable exposure throughout the treatment with lower C_{max} in the first 2 cycles. Specifically, the C1D1 dose of 5 mg was selected since the projected C_{max} of 5 mg mosunetuzumab via SC injection is similar to 1 mg mosunetuzumab via IV infusion, a recommended C1D1 dose of mosunetuzumab when administered IV with step-up dosing. The C1D1 dose of 5 mg was confirmed to be a safe dose in the SC fixed-dose escalation. The C1D15 and C2D1 doses at 45 mg SC are lower than the cleared IV dose of 60 mg IV. The C1D8 dose of 15 or 45 mg is expected to further optimize the benefit–risk profile during step-up dosing with SC administration. The maintenance dose was selected at 45 mg SC, which is projected to provide lower C_{max} but higher exposure at steady state than 30 mg IV and is thereby associated with maintaining sufficient exposure for efficacy and potentially a lower risk of CRS. The Cohort F2 is evaluating the dosing schedule 5/45/45 mg.

In Study GO29781 Group F, mosunetuzumab SC step-up dosing was shown to achieve a higher target dose without compromising the safety profile. As of 2 June 2021, Group F enrolled 71 participants total, of which 67 participants completed Cycle 1. Thirteen (19.4%) and 9 participants (13.4%) experienced Grade 1 and Grade 2 CRS, respectively (according to Lee grades [Lee et al. 2014]). In Group F1 (5/15/45 mg, n=34), CRS occurred after C1D1 (any grade in 25%, Grade 1 in 20%, and Grade 2 in 5%); C1D8 (any grade in 9%, Grade 1 in 6%, and Grade 2 in 3%); and after C1D15 (any grade in 17%, Grade 1 in 11%, and Grade 2 in 6%), which is similar to what was observed in the IV step-up-dosing regimen. In Group F2 (5/45/45 mg, n=33), CRS was observed after C1D1 (any grade in 9%, Grade 1 in 3%, and Grade 2 in 6%) and after C1D8 (any grade in 9%, Grade 1 in 3%, and Grade 2 in 6%). No CRS events were observed after C1D15 in Group F2. No Grade 3 or higher CRS events were reported in either Group F1 or F2. There were no DLT events in either of the dose escalation Cohorts F1 or F2.

Based on these clinical data, both the 5/15/45 mg and 5/45/45 mg dosing regimens for the mosunetuzumab SC dose are considered to have an acceptable safety profile. Compared with mosunetuzumab administered IV, mosunetuzumab administered SC does not have new safety signals except for injection site reactions, which occurred in 33 participants (49.2%), including 31 participants (46.2%) with Grade 1 events and 3 participants (4.4%) with Grade 2 events. The 5/45/45 mg dosing regimen showed comparable safety profiles to the 5/15/45 mg dosing regimen but with a shortened window of CRS, with Grade 2 events being associated with the first two doses of mosunetuzumab during Cycle 1. Further, the 5/45/45 mg dosing regimen also allows faster achievement of target dose. Therefore, this dose is considered the preferred dose for mosunetuzumab SC monotherapy and was chosen as a recommended Phase II dose in Study GO29781 and will be applied to this study combined with either tiragolumab alone (Arm 1) or with tiragolumab and atezolizumab (Arm 2).

4.3.2 Rationale for Tiragolumab Dose and Schedule

The proposed dose of tiragolumab is 600 mg administered by IV infusion on Day 1 of each 21-day cycle (Q3W). The fixed dose of 600 mg IV Q3W is the recommended Phase II dose in solid tumors and was selected on the basis of available clinical PK, biomarker, safety, and preliminary efficacy data from the combined Phase Ia/Phase Ib study (Study GO30103), with single-agent tiragolumab or tiragolumab combined with atezolizumab in solid tumors. In both the Phase Ia portion of Study GO30103 with tiragolumab as a single agent and in the Phase Ib portion with tiragolumab in combination with atezolizumab, the MTD was not reached, and no DLTs were observed in dose escalation at doses of tiragolumab ranging from 2–1200 mg. Complete occupancy of peripheral TIGIT receptors on CD4+, CD8+, and NK cells was observed beginning at 30 mg of tiragolumab in both the Phase Ia and Phase Ib portions of the study and remained sustained at all higher doses (Roche unpublished data). As single agent, prolonged stable disease was observed in participants in the Phase Ia portion of the study at tiragolumab doses beginning at 400 mg. In the Phase Ib portion of the study with tiragolumab plus atezolizumab, anti-tumor activity, as measured by radiographic PRs, was observed across doses for tiragolumab beginning at 30 mg and ranging up to 600 mg in combination with atezolizumab 1200 mg Q3W. Tiragolumab at the same fixed dose of 600 mg IV Q3W has been evaluated as single agent and in combination with rituximab in the Phase Ia/Ib Study GO41036 in participants with R/R NHL. Preliminary safety data from this study suggests that single agent tiragolumab and the combination of tiragolumab with rituximab are acceptable in the participants with R/R NHL. In participants with NHL who were considered safety-evaluable, all treatment-emergent adverse events were Grade 1 or 2. No participants experienced tiragolumab-related adverse events that lead to study treatment discontinuation. Refer to the Tiragolumab Investigator's Brochure for further details regarding the clinical safety profile seen in Study GO41036.

4.3.3 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® USPI).

Atezolizumab 1200 mg Q3W in combination with escalating doses of mosunetuzumab is currently under investigation in Study GO29781 in participants with R/R NHL, where atezolizumab is given on the same-day with mosunetuzumab beginning at Cycle 2. At the highest evaluated dose level (mosunetuzumab IV dose of 1/2/60/30 mg and atezolizumab at 1200 mg), the MTD was not reached. Preliminary clinical data suggested comparable and tolerable safety profiles including frequencies of CRS similar to that of mosunetuzumab as single agent.

Refer to the Atezolizumab Investigator's Brochure for further details on the nonclinical and clinical pharmacology and clinical safety of atezolizumab.

4.3.4 Rationale for Dose-Finding Schedules

During the Phase Ib dose-finding phase, Cohorts A and B will test alternate doses and schedules of mosunetuzumab and tiragolumab. Cohort A will test the safety and tolerability of both agents administered on C1D1. Evaluating the co-administration of mosunetuzumab and tiragolumab beginning in Cycle 1 allows for maximum benefit for participants based on the hypothesized synergies between the drugs early on in the treatment course. This is further supported by the safety–risk profile of mosunetuzumab, the beneficial safety profile that tiragolumab has shown in monotherapy and in combination with rituximab (see Section 2.3), and the low number of potential overlapping toxicities. Potential overlapping toxicities expected with concurrent administration of these agents are summarized in Section 2.3 (Benefit–Risk Assessment) and in Section A6–2. Cohort B will test the safety and tolerability of sequential dosing starting with mosunetuzumab on C1D1 and delayed introduction of tiragolumab on C2D1, to potentially mitigate against overlapping toxicities, if necessary. The rationale for the Cohort B schedule is that CRS, if it occurs, is typically observed during the step-up dosing in Cycle 1. This is based on experience from mosunetuzumab IV administration with step-up dosing in the Study GO29781, where 88% of CRS events occurred during Cycle 1 and 12% occurred in Cycle 2 or later. If CRS is exacerbated by concurrent dosing with tiragolumab during Cycle 1, the delayed start of tiragolumab would mitigate any potential increase in frequency or severity of CRS.

Cohort E will evaluate the combination of mosunetuzumab with tiragolumab and atezolizumab. The schedule and dose for the combination of mosunetuzumab with tiragolumab will be based on the schedule determined during the Safety Run-In Phase of Arm 1. The schedule for the addition of atezolizumab is based on the experience of Group E in the Study GO29781, in which mosunetuzumab IV started with step-up dosing in Cycle 1 and the first dose of atezolizumab was administered in Cycle 2.

4.4 RATIONALE FOR MANDATORY HOSPITALIZATION WITH FIRST ADMINISTRATION OF MOSUNETUZUMAB AND TIRAGOLUMAB OR MOSUNETUZUMAB, TIRAGOLUMAB, AND ATEZOLIZUMAB

Treatment-emergent toxicities, notably CRS, have been observed with mosunetuzumab. These toxicities generally occur upon first exposure to mosunetuzumab. Although the mechanisms of action of these toxicities are not completely understood, it is believed that they are the result of immune cell activation resulting in inflammatory cytokine release. Laboratory and clinical manifestations of cytokine release occur within several days of treatment and decrease in frequency and severity over time.

Based on a favorable safety profile, hospitalization is not mandatory for mosunetuzumab SC monotherapy with the 5/45/45 mg dosing schedule in the expansion cohorts of Study GO29781 (Group F), which is the dosing schedule that will be used in this study. On the basis of a potential increase in the rate and severity of CRS when

check point inhibitor is added to mosunetuzumab treatment (see Section 4.3.1 and the Mosunetuzumab Investigator's Brochure for details), hospitalization will be required for all participants enrolled in Safety Run-In Cohorts when mosunetuzumab is administered in combination with tiragolumab for the first time in Arm 1 or when mosunetuzumab, tiragolumab, and atezolizumab are administered in combination for the first time in Arm 2. The hospitalization will be for at least 72 hours following the end of the last study drug administration on the respective day. Participants are not required to be hospitalized at other timepoints; however, investigators may choose to hospitalize a participant following any mosunetuzumab dose for close monitoring if indicated based on their clinical judgment.

The requirements for hospitalization in the expansion arms will be discontinued if no CRS Grade $\geq$3 is observed in 6 DLT-evaluable participants in the respective Safety Run-In Cohort that evaluated the same dose and schedule.

4.5 RATIONALE FOR THE TREATMENT OF CRS USING TOCILIZUMAB

Cytokine release syndrome is caused by the excessive release of cytokines by immune effector or target cells during an exaggerated and sustained immune response. Cytokine release syndrome can be triggered by a variety of factors, including infection with virulent pathogens, or by medications that activate or enhance the immune response, resulting in a pronounced and sustained immune response.

Regardless of the inciting agent, severe or life-threatening CRS is a medical emergency. If recognition or management is delayed, it can result in significant disability or fatal outcome. Current clinical management focuses on providing supportive care, treating the individual signs and symptoms, and attempting to dampen down the inflammatory response using high-dose corticosteroids. However, this approach is not always successful, especially in the case of late intervention.

Cytokine release syndrome is associated with elevations in a wide array of cytokines, including marked elevations in IFN-γ, IL-6, and tumor necrosis factor (TNF)-α levels. Emerging evidence implicates IL-6 as a central mediator in CRS. IL-6 is a pro-inflammatory multi-functional cytokine produced by a variety of cell types, which has been shown to be involved in a diverse array of physiological processes including T cell activation. Regardless of the inciting agent, CRS is associated with high IL-6 levels, and IL-6 correlates with the severity of CRS with participants who experience severe or life-threatening CRS (CTC Grades 3 or higher) having much higher IL-6 levels compared with their counterparts who do not experience CRS or experience milder CRS reactions (CTC Grades 0–3; Panelli et al. 2004; Lee et al. 2014; Doessegger and Banholzer 2015; Chen et al. 2016).

Tocilizumab (Actemra®/RoActemra®) is a recombinant, humanized, anti-human monoclonal antibody directed against soluble and membrane-bound IL-6R,

which inhibits IL-6 mediated signaling. Blocking the inflammatory action of IL-6 using tocilizumab could therefore represent a novel approach for the treatment of CRS. Refer to the Tocilizumab Investigator's Brochure for additional nonclinical and clinical information regarding tocilizumab.

Cytokine release syndrome is observed with T cell-recruiting therapies including CAR T cell therapy and bispecific molecules such as blinatumomab. There have been multiple reports in the literature of tocilizumab being used off-label to successfully treat severe or life-threatening CRS, and tocilizumab is now approved in some countries for the treatment of CAR T cell–induced severe or life-threatening CRS in adults and pediatric patients 2 years of age and older (Teachey et al. 2013; Lee et al. 2014; National Institutes of Health 2015; Lee et al. 2019).

Taken together, these findings indicate that participants treated with mosunetuzumab who develop CRS may benefit from tocilizumab therapy. See Section A6–2.3.1 for management guidelines for CRS.

4.6 INTERNAL MONITORING COMMITTEE

An IMC will be formed during the study to make recommendations on study conduct based on trial safety data to ensure enhanced patient safety while receiving study treatment. The IMC will consist of an IMC Medical Monitor Chair external to the study team and Sponsor's representatives from Clinical Science, Safety Science, and Biostatistics who are all external to the study team. The IMC will convene to review cumulative safety data, including but not limited to the incidence and nature of serious adverse events, deaths, Grade ≥3 adverse events, and adverse events of special interest. The IMC will be convened after 6 participants complete the DLT Assessment Period or if 2 participants develop a DLT in a Safety Run-In Cohort. There will be another review of safety data by the IMC in each arm after an additional 6 patients have been enrolled in the expansion cohorts, as described in Section 4.1.2.1. This analysis will include all participants in that arm treated at the dose and schedule chosen for the expansion cohorts. Planned interim analyses will be performed according to Section 9.5. The IMC may also be convened ad hoc and at the request of the Medical Monitor.

The IMC will operate according to a prespecified charter that will outline the IMC members, roles, responsibilities, and communication processes. The IMC may further make recommendations regarding study conduct, including but not limited to the following: performing additional safety analyses, modification of hospitalization and premedication requirements, amending the study protocol, holding enrollment pending further safety evaluations, enrolling additional participants at a specific dose level and schedule to obtain additional safety data, holding or discontinuing study treatment, or terminating the study.

4.7 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last scheduled procedure or visit shown in the schedule of activities (see Section 1.3).

The end of this study is defined as the date of the last scheduled procedure of the last participant in the study shown in the schedule of activities for the last participant in the study globally or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur about 36 months after the last participant is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

4.8 DURATION OF PARTICIPATION

Treatment will continue for a total of 8 treatment cycles if a CR is achieved at PRA, or for 17 cycles if response is assessed as PR or SD at PRA as determined by the Lugano classification (Cheson et al. 2014; Appendix 10). Treatment will be discontinued if there is confirmed disease progression or unacceptable toxicity.

The total duration of study participation for each individual is expected to range from 1 day to more than 36 months.

5. STUDY POPULATION

Approximately 6–118 participants with R/R B-cell NHL will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

- Participants who are capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the Informed Consent Form and in this protocol
- Participants who are age ≥ 18 years at the time of signing the Informed Consent Form
- Participants who are able to comply with the study protocol and procedures and required hospitalizations, in the investigator's judgment
- Participants who have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Participants who have a life expectancy of at least 12 weeks
- Participants who have histologically documented FL or DLBCL

- That has relapsed or failed to respond to at least two prior systemic treatment regimens and for which no suitable therapy of curative intent or higher priority exists (e.g., standard chemotherapy, ASCT, CAR T cells)

  Including at least one line of therapy containing a CD20-directed therapy

  Including at least one prior regimen containing anthracycline for participants with DLBCL, HGBL, trFL, and FL Grade 3b

  Including at least one prior regimen containing an alkylating agent for participants with FL

  Bridging therapy followed by CAR T cell therapy will be counted as one line of therapy.

  Local therapies (e.g., radiotherapy or intrathecal therapy) will not be considered as lines of therapy.
- That expresses CD20 as determined by the local laboratory
- That are included in the following list of diagnoses by 2016 WHO classification of lymphoid neoplasms:

  FL (including in situ follicular neoplasia and duodenal-type FL)

  Pediatric-type FL

  DLBCL, NOS (including germinal center B-cell type and activated B-cell type)

  T-cell/histiocyte–rich large B-cell lymphoma

  High grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements

  High grade B-cell lymphoma, NOS

  EBV+DLBCL, NOS

  HHV8+DLBCL, NOS

  Anaplastic lymphoma kinase+large B-cell lymphoma
- Transformed FL is an eligible diagnosis if the disease histology after transformation is DLBCL or HGBCL.

  Participants must be R/R to standard therapies for transformed FL.

  Participants with Richter's transformation are not eligible for enrollment into the study.
- Participants with FL grade 3b are eligible for enrollment into only the Safety Run-In Cohorts A, B, and E and Expansion Cohort D if they are R/R to standard therapies for aggressive NHL.
- See Section 4.1 of the protocol for information on which cohorts will enroll which disease histologies.
- The Sponsor may limit the number of participants with particular NHL subtypes enrolled in the study.

- Participants who have at least one bi-dimensionally measurable (> 1.5 cm) nodal lesion or at least one bi-dimensionally measurable (> 1.0 cm) extranodal lesion
- Participants who have confirmed availability of a tumor tissue (a newly collected tumor tissue sample obtained at baseline is preferred; if a fresh biopsy is unobtainable per investigator assessment, archival tissue is acceptable). See Section 8.7 for specimen requirements.
- Participants with FL (including trFL) for whom a bone marrow biopsy and aspirate can be collected
- Participants with adequate hematologic and organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (C1D1):
  - AST and ALT ≤ 2.5 × ULN
  - Total bilirubin ≤ 1.5 × ULN

    Participants with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.
  - INR ≤ 1.5 × ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT ≤ 1.5 × ULN in the absence of lupus anticoagulant and in the absence of therapeutic anticoagulation
  - Measured or estimated creatinine clearance ≥ 50 mL/min by institutional standard method
  - Platelet count ≥ 75,000/μL in the absence of platelet transfusion within 72 hours
  - Total hemoglobin ≥ 9 g/dL without transfusion within 21 days
  - Absolute neutrophil count (ANC) ≥ 1000/μL

    Participants must not have received growth factor within the previous 7 days prior to the ANC used for eligibility.
  - For participants who do not meet criteria for hematologic function because of extensive marrow involvement of NHL and/or disease-related cytopenias (e.g., immune thrombocytopenia) may be enrolled into the study if each of the below criteria are met:

    Platelet count ≥ 50,000/μL without transfusion within 14 days

    ANC ≥ 500/mm^3

    Any hemoglobin but without transfusion within 7 days
- For women of childbearing potential: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 3 months after the final dose of mosunetuzumab, 3 months after the final dose of tiragolumab, 5 months after the last dose of atezolizumab (if applicable), and 3 months after

the last dose of tocilizumab (if applicable), whichever is longer. Women must refrain from donating eggs during this same period.

- A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
- Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:
  - With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of tiragolumab, and 2 months after the final dose of tocilizumab (if applicable), to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

- Participants who are pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of mosunetuzumab, 3 months after the final dose of tiragolumab, 5 months after the last dose of atezolizumab (if applicable), and 3 months after the last dose of tocilizumab (if applicable), whichever is longer

- Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Participants who have received any of the following treatments prior to study entry:
  - Treatment with mosunetuzumab or other CD20/CD3–directed bispecific antibodies
  - Treatment with tiragolumab or other anti-TIGIT agent
  - Allogeneic SCT
  - Solid organ transplantation
- Participants who received any of the following treatments, whether investigational or approved, within the respective time periods prior to initiation of study treatment:
  - Radiotherapy within 2 weeks prior to the first dose of study treatment

    If participants have received radiotherapy within 4 weeks prior to the first study treatment administration, participants must have at least one measurable lesion outside of the radiation field.
  - Autologous SCT within 100 days prior to first study treatment
  - CAR T-cell therapy within 30 days before first study treatment
  - Use of monoclonal antibodies or antibody-drug conjugates for the treatment of lymphoma within 4 weeks prior to first study treatment
  - Use of radioimmunoconjugates within 12 weeks prior to first study treatment
  - Systemic immunosuppressive medications (including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor agents) within 2 weeks prior to first dose of study treatment

    Systemic corticosteroid treatment $\leq$10 mg/day prednisone or equivalent and inhaled corticosteroids are permitted.

    Administration of acute, low-dose, systemic immunosuppressant medications (e.g., single dose of dexamethasone for nausea or B symptoms) is permitted.

    The use of mineralocorticoids for management of orthostatic hypotension and corticosteroids for management of adrenal insufficiency is permitted.
  - Any other anti-cancer therapy, whether investigational or approved, including but not limited to chemotherapy, within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to initiation of study treatment
  - The Medical Monitor should be informed of any prior cancer immunotherapy not explicitly described in this protocol.
- Participants who received a live, attenuated vaccine within 4 weeks before first dose of study treatment, or in whom it is anticipated that such a live attenuated vaccine will be required during the study period or within 5 months after the final dose of study treatment

- Participants with aggressive NHL who are currently eligible for autologous SCT
- Participants with current or past history of CNS lymphoma or leptomeningeal infiltration
- Participants with a history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
- Participants with a contraindication to atezolizumab (specific to Arm 2 of the study) or tocilizumab
- Participants in whom clinically significant toxicities from prior treatment have not resolved to Grade ≤ 1 (per NCI CTCAE v5.0) prior to the first study drug administration with the following exceptions:
  - Grade 2 peripheral sensory or motor neuropathy
  - Any grade alopecia or vitiligo
  - Endocrinopathy managed with replacement therapy
- Participants with treatment-emergent immune-mediated adverse events associated with prior immunotherapeutic agents as follows:
  - History of a Grade ≥ 3 immune-mediated adverse event attributed to prior immune checkpoint-inhibitor (ICI) therapy (other than endocrinopathy managed with replacement therapy or asymptomatic elevation of serum amylase or lipase)
  - All immune-mediated adverse events related to prior cancer immunotherapy (other than endocrinopathy managed with replacement therapy, stable vitiligo, and stable cytopenias that meet the inclusion criteria) must have resolved to baseline.
  - Participants treated with corticosteroids for immune-mediated adverse events must demonstrate absence of related symptoms or signs for ≥ 4 weeks following discontinuation of corticosteroids.
- Participants with evidence of any significant, concomitant disease that could affect compliance with the protocol or interpretation of results, including but not limited to:
  - A history of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:

    Any of the following malignancies previously curatively treated: carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal, or squamous cell skin cancer

    Prostate cancer with no evidence of metastatic disease and not on active therapy except for anti-androgen therapy.

    Participants with any other malignancy appropriately treated with curative intent and in remission without treatment for ≥ 2 years prior to enrollment are eligible.

- Significant cardiovascular disease (e.g., New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmia, or unstable angina)
- Significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm)
- Clinically significant history of liver disease, including viral or other hepatitis, or cirrhosis
- Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease

  Participants with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 1 year and have no residual neurologic deficits as judged by the investigator are allowed.

  Participants with a history of epilepsy who have had no seizures in the past 2 years with or without anti-epileptic medications can be eligible only in the Expansion Cohorts C, D and F.
- History of confirmed progressive multifocal leukoencephalopathy
- Known active bacterial, viral (including SARS-CoV-2), fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization within 4 weeks (relating to the completion of the course of antibiotics) prior to first study treatment administration
- Positive serologic HIV test at screening
- Positive test results for chronic hepatitis B infection (defined as positive hepatitis B surface antigen [HBsAg] serology)

  Participants with occult or prior hepatitis B infection (defined as positive total hepatitis B core antibody and negative HBsAg) may be included if HBV DNA is undetectable at the time of screening. These participants must be willing to undergo monthly DNA testing and appropriate antiviral therapy as indicated.

  Acute or chronic HCV infection

  Participants who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.
- Known or suspected chronic active EBV infection
- Known or suspected history of HLH
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, granulomatosis *with polyangiitis*, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 13)

Participants with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.

Participants with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

Participants with a history of disease-related immune thrombocytopenic purpura or autoimmune hemolytic anemia may be eligible.

Participants with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

Rash must cover ≤10% of body surface area.

Disease is well controlled at baseline and requires only low-potency topical corticosteroids.

No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

Participants with transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent, such as acute Lyme arthritis, may be eligible. The Medical Monitor is available to advise as needed.

- Participants who underwent recent major surgery within 4 weeks prior to first study treatment administration, with the exception of protocol-mandated procedures (e.g., tumor biopsies and bone marrow biopsies)

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions.

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no additional activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per individual) at

the investigator's discretion. Individuals are not required to re-sign the consent form if they are re-screened within 28 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log (see Section 8).

5.5 CRITERIA FOR TEMPORARILY DELAYING ADMINISTRATION OF STUDY INTERVENTION

See Appendix 6, Section A6–2.1 for study treatment interruption guidelines.

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

The investigational medicinal products (IMPs) for this study are mosunetuzumab, tiragolumab, atezolizumab, and tocilizumab. Any pre-medications (e.g., corticosteroids) are considered non-investigational medicinal products.

6.1 STUDY TREATMENTS ADMINISTERED

Table 5 provides a description of assigned study treatments for this study.

Table 5 Study Treatment Description

	Mosunetuzumab	Tiragolumab	Atezolizumab	Tocilizumab
Use	Experimental	Experimental	Experimental	Other
Type of medicinal product	IMP	IMP	IMP	IMP
Drug form	Refer to the Pharmacy Manual and Investigator's Brochure.			
Unit Dose Strength(s)				
Packaging				
Formulation(s)				
Dosage Level(s)	C1D1: 5 mg C1D8: 45 mg C1D15: 45 mg C2+D1: 45 mg	600 mg Q3W	1200 mg Q3W	See Appendix 8
Route of administration	SC injection	IV	IV	IV
Source	Sponsor	Sponsor	Sponsor	Sponsor or Site [a]

C = cycle; D = day; IMP = investigational medicinal product; Q3W = every 3 weeks.

[a] Tocilizumab may be obtained locally by the study sites for emergency purposes if permitted by local regulations and will be formulated, prepared, and handled according to standard practice.

The treatment regimens are summarized in Section 4.1.

Guidelines for dose modification and treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 6.

On days when two or more of the IMPs are given, the order of the administration should be mosunetuzumab, tiragolumab with an intervening observation period (see Section 6.1.2), and atezolizumab (if applicable).

Administration of study treatments will be performed in a monitored setting with immediate access to trained critical care personnel and facilities and adequate equipment to respond to and manage potentially serious reactions and medical emergencies.

For anaphylaxis precautions, see Appendix 7. For management of infusion-related reactions, including guidance on premedication, please see Section 6.1.1.

6.1.1 Mosunetuzumab

Flat dosing independent of body weight will be used for mosunetuzumab. The starting dose of mosunetuzumab in Cohort A will be 5 mg/45 mg/45 mg (dose levels on C1D1/C1D8/C1D15) as determined in Study GO29781. The dose on C2D1 and on D1 of subsequent cycles will be the same as the C1D15 dose.

When administered SC, mosunetuzumab will be delivered by standard medical syringe with a final volume not to exceed 2.0 mL. Compatibility testing has shown that mosunetuzumab is stable in extension sets and polypropylene syringes.

Mosunetuzumab will be administered to well-hydrated participants. Corticosteroid premedication with dexamethasone 20 mg (preferred) or 80 mg methylprednisolone should be administered orally or intravenously prior to the administration of each mosunetuzumab dose on dosing days in Cycle 1 (e.g., C1D1, C1D8, and C1D15). The administration of corticosteroid premedication may be optional for Cycle 2 and beyond based on the investigator's assessment. The use of an alternative corticosteroid compound (e.g., due to unavailability of dexamethasone or methylprednisolone) is only permitted after consultation with the Medical Monitor at the time of enrollment. However, if the participant experiences CRS with prior administration of mosunetuzumab, premedication with steroids must be administered for subsequent doses until no additional CRS events are observed. In addition, premedication with oral acetaminophen or paracetamol (e.g., 500–1000 mg) and/or 50–100 mg diphenhydramine may be administered per standard institutional practice prior to administration of mosunetuzumab.

Vital signs should be assessed prior to each mosunetuzumab injection (within 30 minutes prior to injection). Mosunetuzumab will be administered by qualified staff

over 30 seconds to 2 minutes. Refer to the Pharmacy Manual for more details including syringe size and preferred injection site. All participants must have an IV access in place prior to mosunetuzumab SC administration for at least the first 2 cycles. Following the first administration of mosunetuzumab, participants will be observed for at least 30 minutes for fever, chills, rigors, hypotension, nausea, or other signs and symptoms of CRS after the mosunetuzumab administration. Participants should also be observed for 30 minutes after injection for subsequent doses if a CRS event occurred with the previous dose. The observation time may be shortened to 15 minutes for subsequent doses if no CRS occurred with the previous dose. Vital signs should be recorded every 15 (±10) minutes during this observation period (for 30 minutes following the first mosunetuzumab injection and 15 minutes for subsequent doses if no CRS occurred with the previous dose). Thereafter, vital signs should be monitored every 4 hours until discharge. If required by the infusion guidelines for the other study drugs (Sections 6.1.2 and 6.1.3), additional vital sign measurements should be taken.

Guidelines for mosunetuzumab dosage and schedule modification and treatment interruption or discontinuation are provided in Appendix 6, Section A6–2.

Hospitalization requirements for participants receiving study treatment are described in Section 4.4. Guidelines for medical management of injection-site reactions are provided in Appendix 6. The recommended management of CRS is detailed in Appendix 6, Section A6–2.3.1.

6.1.2 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle starting in Cycle 1 or Cycle 2 per the instructions outlined in Table 6. For details on the respective dosing schema in each cohort, see Section 4.1 and the study schema in Section 1.2.

On days when tiragolumab is given in combination with mosunetuzumab (with or without atezolizumab), tiragolumab will be administered after the end of the observation period for mosunetuzumab.

No individual dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation of tiragolumab and guidance on study drug administration in the context of management of specific adverse events is provided in Appendix 6, Section A6–2.

Table 6 Administration of First and Subsequent Infusions of Tiragolumab

	First Infusion	Subsequent Infusions
Before infusion of tiragolumab	• Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion.	• If the participant experienced an IRR during any previous infusion of tiragolumab, premedication with an antihistamine and/or antipyretic may be administered for subsequent doses, at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the tiragolumab infusion.
Infusion of tiragolumab	• Tiragolumab should be infused over 60 (± 15) minutes. • Vital signs should be recorded every 15 (± 5) minutes during the infusion.	• Tiragolumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) minutes if the participant experienced an infusion-related reaction with the previous infusion. • Vital signs should be recorded during the infusion if clinically indicated.
Observation period after infusion of tiragolumab	• After the infusion of tiragolumab, the participant begins a 60-minute observation period. • Vital signs should be recorded at 30 (± 10) minutes after the infusion of tiragolumab. • Participants will be informed about the possibility of delayed postinfusion symptoms and will be instructed to contact their study physician if they develop such symptoms.	• If the participant tolerated the previous infusion of tiragolumab well without infusion-associated adverse events, the observation period may be reduced to 30 minutes. • If the participant experienced an infusion-associated adverse event in the previous infusion, the observation period should be 60 minutes. • If clinically indicated, vital signs should be recorded at 30 (± 10) minutes after the infusion of tiragolumab. • Participants will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact their study physician if they develop such symptoms.

IRR = infusion-related reaction.

6.1.3 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle starting in Cycle 2 per the instructions outlined in Table 7 in Cohorts E and F. For details on the respective dosing schema in each cohort see Section 4.1 and the study schema in Section 1.2.

On days when atezolizumab is given in combination with mosunetuzumab and tiragolumab, atezolizumab will be administered after the end of the observation period for tiragolumab.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab for treatment interruption or discontinuation are provided in Appendix 6 (Section A6–2). Guidance on study drug administration in the context of management of specific adverse events is provided in Section A6–2.

Table 7 Administration of First and Subsequent Infusions of Atezolizumab

	First Infusion	Subsequent Infusions
Before infusion of atezolizumab	• Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion.	• If the participant experienced an IRR with any previous infusion of atezolizumab, premedication with an antihistamine and/or antipyretic medication may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion.
Infusion of atezolizumab	• Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be recorded every 15 (± 5) minutes during the infusion.	• Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an IRR or 60 (± 15) minutes if the participant experienced an IRR with the previous infusion. • If clinically indicated, vital signs should be recorded during the infusion.

IRR = infusion-related reaction.

Table 7 Administration of First and Subsequent Infusions of Atezolizumab (cont.)

	First Infusion	Subsequent Infusions
Observation period after infusion of atezolizumab	• After the infusion of atezolizumab, the participant begins a 60-minute observation period. • Vital signs should be recorded at 30 (±10) minutes after the infusion of atezolizumab. • Participants will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the participant tolerated the previous atezolizumab infusion well without infusion-associated adverse events, the observation period after the next and following infusions may be reduced to 30 minutes. • If the participant experienced infusion-associated adverse events in the previous infusion, the observation period should be 60 minutes. • If clinically indicated, vital signs should be recorded at 30 (±10) minutes after the infusion of atezolizumab.

IRR = infusion-related reaction.

6.1.4 Tocilizumab

Tocilizumab (Actemra/RoActemra) is a recombinant, humanized, anti-human monoclonal antibody directed against soluble and membrane-bound IL-6 receptor, which inhibits IL-6–mediated signaling. Tocilizumab will be administered as a rescue IMP when necessary, to participants who experience a CRS event (see Appendix 3 and Appendix 8). Tocilizumab will be supplied by the Sponsor as an IMP and information on the formulation and handling of tocilizumab will be provided in the Pharmacy Manual and the Tocilizumab Investigator's Brochure. Due to the need to manage CRS urgently and potential accessibility limitations at the site, commercial tocilizumab may be obtained locally by the study sites for emergency purposes if permitted by local regulations and will be prepared, handled, and managed according to standard institutional practices. Refer to the local prescribing information for further instructions regarding recommended storage conditions and packaging configuration.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using an interactive voice or web-based response system (IxRS) to confirm the shipment

condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

All tocilizumab used in the study will be tracked and accounted for as required by International Council for Harmonisation GCP. Tocilizumab supplied by the Sponsor will include a clinical study drug/IMP label. Commercial tocilizumab obtained locally by the study site will have the marketed product label. Refer to the local prescribing information for further instructions regarding recommended storage conditions and packaging configuration, as well as the study Pharmacy Manual and Tocilizumab Investigator's Brochure.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the Pharmacy Manual and/or the mosunetuzumab, tiragolumab, atezolizumab, or tocilizumab Investigator's Brochure or local prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

6.3.1 Treatment Assignment

This is a non-randomized, open-label study. Participants will be assigned to study cohorts based on tumor type in the order in which they are enrolled. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an IxRS. Details regarding the screening and enrollment processes for this study are described in the Cohort Management Plan.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the electronic Case Report Form (eCRF). The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.5 DOSE MODIFICATION

There will be no dose modifications for atezolizumab and tiragolumab in this study.
The dose of mosunetuzumab can be reduced for management of CRS, as described in Appendix 6.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer continued access to Roche IMPs (mosunetuzumab, tiragolumab, and atezolizumab, if applicable) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMPs (mosunetuzumab, tiragolumab, and atezolizumab, if applicable) after completing the study if all of the following conditions are met:

- The participant has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the participant.
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A participant will not be eligible to receive Roche IMPs (mosunetuzumab, tiragolumab, and atezolizumab, if applicable) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for B-cell NHL.
- The Sponsor has reasonable safety concerns regarding the IMP as a treatment for B-cell NHL.
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor on the basis of clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the study completion/discontinuation visit must be recorded on the Concomitant Medications and associated eCRF(s) along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.3 and taking into account cautionary therapies defined in Section 6.8.2. Participants who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should

be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Section A6-2.3.3).

Use of the following concomitant therapies is permitted as described below:

- Premedication with antihistamines, anti-pyretics, and/or analgesics may be administered at the discretion of the investigator (see Section 6.1)
- Oral contraceptives with a failure rate of <1% per year (see Section 5.1)
- Hormone-replacement therapy
- Treatment of CRS according to Appendix 6, Section A6–2.3.1
- Treatment of HLH according to published recommendations and/or institutional practice (see Appendix 6, Section A6–2.3.3)
- TLS prophylaxis/therapy according to published recommendations and/or institutional practice (see Appendix 6, Section A6–2.3.6)
- Anti-emetic prophylaxis/therapy according to published recommendations and/or institutional practice
- Prophylactic and therapeutic use of G-CSF (filgrastim, pegfilgrastim) is allowed in accordance with instructions provided in the package inserts, institutional practice, and/or published guidelines (Smith et al. 2015). Growth factor support should be started when ANC is below 500/mm^3, unless medically contraindicated.
- Non-live vaccinations
- Concomitant use of other hematopoietic growth factors such as erythropoietin, granulocyte/macrophage colony–stimulating factor (sargramostim), or thrombopoietin (oprelvekin, eltrombopag) is allowed in accordance with instructions provided in the package inserts, institutional practice, and/or published guidelines.
  - In the Safety Run-In Cohorts, they should not be initiated or increased in dose from the start of the screening period until the completion of the DLT Assessment Period in the absence of a DLT or until a DLT occurs.

6.8.1.1 Infection Prophylaxis

Anti-infective prophylaxis for viral, fungal, bacterial, or Pneumocystis infections is permitted and should be instituted per institutional practice or investigator preference based on individual participant risk factors. Participants in countries where prophylactic antiviral medications for hepatitis B reactivation are the standard of care may be treated prophylactically (Taplitz et al. 2018; National Comprehensive Cancer Network 2020).

Investigators should highlight to study participants the precautions that can prevent or mitigate SARS-CoV-2 infections (e.g., masking, social distancing, avoiding close contact with anyone infected with SARS-CoV-2, and informing their health care provider or general practitioner about close contacts and/or at first signs of infection).

Administration of COVID-19 prophylaxis using available agents in accordance with local institutional guidance (including but not limited to vaccines and monoclonal

antibodies) is recommended (El Chaer et al. 2022). Please see Sections 2.3.1 and 6.8.4.1 for additional considerations around concomitant administration of COVID-19 vaccines and treatment interruption.

In the event of new-onset SARS-CoV-2 infection during study treatment, appropriate therapy using available agents in accordance with local institutional guidance (including but not limited to antivirals and/or monoclonal antibodies) is also recommended (El Chaer et al. 2022).

6.8.2 Cautionary Therapy

6.8.2.1 Medications Given with Precaution Due to Effects Related to Cytochrome P450 Enzymes

Mosunetuzumab

Given the expected pharmacology of mosunetuzumab, the transient release of cytokines (most resolved within the first 24 hours of the C1D1 dose) may suppress CYP450 enzymes and cause drug–drug interactions. Preliminary clinical data indicate that mosunetuzumab induced a transient elevation in plasma IL-6, with peak levels occurring in the majority of participants within 4–6 hours of the C1D1 dose and returning to baseline by 24 hours. Participants at highest risk of a drug–drug interaction are those receiving concomitant medications that are CYP450 substrates and have a narrow therapeutic index (Appendix 12). Such concomitant medications should be monitored for toxicity and dose adjusted accordingly.

Tocilizumab

CYP450 enzymes in the liver are down-regulated by infection and inflammatory stimuli, including cytokines such as IL-6. Inhibition of IL-6 signaling in participants with rheumatoid arthritis who are treated with tocilizumab may restore CYP450 activities to higher levels than those participants not treated with tocilizumab, leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CY2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The effects of tocilizumab on CYP2C8 or transporters are unknown. In vivo studies with omeprazole (metabolized by CYP2C19 and CYP3A4) and simvastatin (metabolized by CYP3A4) showed up to a 28% and 57% decrease in exposure 1 week following a single dose of tocilizumab, respectively.

The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index (see Appendix 12), where the dose is individually adjusted:

- Upon initiation or discontinuation of tocilizumab in participants being treated with these types of medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed.

- Prescribers should exercise caution when tocilizumab is coadministered with CYP3A4 substrate drugs where a decrease in effectiveness is undesirable (e.g., oral contraceptives, lovastatin, atorvastatin).
- The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

6.8.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 6.8.3) may be used during the study at the discretion of the investigator; herbal therapies intended for the treatment of lymphoma are prohibited.

6.8.2.3 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with mosunetuzumab, tiragolumab, and/or atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with tiragolumab and/or atezolizumab therapy (see Appendix 6 for details).

6.8.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including but not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 5.2), and during study treatment, until disease progression is confirmed and documented, and the participant has discontinued study treatment.
  - Contraceptives, hormone-replacement therapy, or megestrol acetate are permitted.
  - Adjuvant endocrine therapy for non-metastatic, hormone receptor–positive breast cancer and anti-androgen therapy for non-metastatic prostate cancer are permitted.
- Biologic or targeted agents for treatment of lymphoma (other than hematopoietic growth factors as described in Section 6.8.1)
- Investigational, unlicensed, or unapproved agents

- CNS prophylaxis
- Live vaccines (e.g., live-attenuated; see Section 6.8.4)
- Immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2
  - These agents, in combination with tiragolumab, could potentially increase the risk for autoimmune conditions.
  - In addition, all participants (including those who discontinue the study early) should not receive other immunostimulatory agents for 5 half-lives (approximately 12 weeks) after the final dose of tiragolumab.

Participants who require the use of any of these agents will be discontinued from study treatment. The above list of medications is not necessarily comprehensive. If questions arise regarding medications not listed above, the Medical Monitor is available to advise as needed.

6.8.4 Immunizations

Participants may not receive either primary or booster vaccination with live virus vaccines for at least 4 weeks before initiation of or at any time during study treatment or after the last dose of study treatment until B-cell ranges recover to normal range. Live, attenuated vaccine should also be avoided within 90 days after the last dose of tiragolumab and within 5 months after the last dose of atezolizumab. Participants who require the use of vaccination with live virus vaccines will be discontinued from study treatment.

Killed vaccines or toxoids should be given at least 4 weeks prior to the first dose of study treatment to allow development of sufficient immunity.

6.8.4.1 COVID-19 Vaccination

Concomitant administration of an approved non-live COVID-19 vaccine is permitted. Examples of permitted vaccines include mRNA, inactivated virus, and replication-deficient viral vector vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

The SITC and National Cancer Comprehensive Network® (NCCN) recommendations along with local and institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. Per recommendations of the NCCN

COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including ICIs), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020).

For participants enrolling in this study and receiving study treatment, a decision whether and when to administer the vaccine to a participant should be made on an individual basis by the investigator in consultation with the participant. In alignment with clinical practice procedures, factors to consider when making the individualized decision for participants receiving study treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the participant and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

Given that the mechanism of action of CD20-targeted therapies leads to B cell depletion, it is expected that the efficacy of COVID-19 vaccines may be diminished. Prior to starting study treatment, COVID-19 vaccines should be administered to participants, with the aim to complete the vaccination course at least one week prior to starting immunosuppressive therapy, unless a delay is clinically unacceptable.

Cytokine release syndrome is a risk for mosunetuzumab that occurs most commonly during step-up dosing. Many COVID-19 vaccines are highly immunogenic, and their risk of potentiating CRS is unknown. If a COVID-19 vaccine is administered while the participant is already receiving study treatment, the administration of the vaccine should be timed to take place after completion of mosunetuzumab step-up dosing and at least one week after administration of the target mosunetuzumab dose. The COVID-19 vaccine should be administered in the middle of a treatment cycle, for example one week before or after a dose of study treatment.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. See the schedule of activities (Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Confirmed disease progression per investigator assessment according to 2014 Lugano Response Criteria for Malignant Lymphoma (see Appendix 10) or symptomatic deterioration attributed to disease progression
- Unacceptable toxicity. See Section A6–2.2 for guidance on treatment interruptions and discontinuation due to toxicity.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants will return to the clinic for a treatment discontinuation visit 30 (±7) days after the final dose of study drug. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

After treatment discontinuation, information on survival status and new anti-cancer therapy will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death (unless the participant withdraws consent, or the Sponsor terminates the study).

See the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). See the

schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

If a participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic and determine if there are ways to support participation.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Collection of any participant samples may be terminated by the Sponsor at any time. The decision to discontinue sample collection will be communicated to sites (including Institutional Review Boards and Ethics Committees [IRBs/ECs]) by means of a memorandum and will not require a protocol amendment.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, will be recorded at baseline. Any medication or vaccines (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded at baseline. Demographic data, including age, sex, and self-reported race/ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

At the time of re-treatment for eligible participants (see Section 4.1.3), the re-screening medical history should include any cancer-related procedures or any adverse events related to mosunetuzumab, tiragolumab, or atezolizumab occurring after initial treatment discontinuation that were not captured by protocol-specified follow-up.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable. Urgent safety

concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Participants will undergo tumor assessments at screening, interim response assessment at the end of Cycle 4 (between C4D15 and C4D21, prior to starting Cycle 5), and PRA at the end of Cycle 8 (between C8D15 and C8D21). Response will be evaluated according to 2014 Lugano criteria (Appendix 10). After PRA, response will continue to be evaluated every 3 months during the first year after treatment initiation, and then every 6 months until the participant develops progressive disease, study discontinuation, and/or the start of new lymphoma treatment, or at any time disease progression is suspected. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and/or evaluable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of physical examinations, CT scans, fluorodeoxyglucose (FDG) PET–CT scans, and bone marrow examinations.

Diagnosis of disease progression based on clinical examination must be confirmed by imaging (e.g., CT scan, FDG PET–CT scan) as soon as feasible (within 30 days) and prior to initiation of non–protocol-specified anti-cancer therapy.

Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria outlined below, and the participant has not received anti-cancer therapy since the assessment.

8.1.1.1 Radiographic Assessments

Fluorodeoxyglucose PET-CT scans, in conjunction with diagnostic-quality CT scans, are required at screening, IRA, and PRA. Following the PRA, CT scans with or without PET should be performed according to the schedule outlined in in the schedule of activities (Section 1.3).

The FDG PET–CT scans should extend from skull base to mid-thigh. Full-body FDG PET–CT scans should be performed when clinically appropriate.

CT scans with contrast (per institutional standard operating procedures) should include the chest, abdomen, and pelvis. CT or magnetic resonance imaging (MRI) scans of other disease sites should be performed as clinically indicated. If a CT scan with contrast is contraindicated (e.g., in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan is permitted if it allows for consistent and precise measurement of target lesions during the study. The MRI scans may be used instead of

CT scans in patients for whom they are contraindicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). Diagnostic contrast-enhanced CT scans obtained as part of a PET-CT scan may be used in lieu of dedicated CT scans.

Radiographic images may be submitted to an Independent Review Facility for a quality and completeness check, for potential review, and for temporary storage prior to transferring them to the Sponsor.

Radiographic images, whether reviewed locally or centrally, must be evaluated by a qualified, certified expert.

8.1.1.2 Bone Marrow Examinations

Participants with DLBCL may use screening PET/CT scans to assess bone marrow involvement; bone marrow examinations are not required unless clinically indicated (Cheson et al. 2014).

Participants with FL or trFL who had bone marrow infiltration at any time prior to study initiation are required to undergo bone marrow examinations at screening (within 90 days prior to initiation of study treatment) for staging purposes.

Participants with FL or trFL are required to undergo repeat bone marrow examinations:

- To confirm a CR if there was tumor-infiltrated bone marrow at screening, within 42 days of the radiologic assessment that shows CR for the first time; or
- To confirm suspected relapse in the bone marrow

Bone marrow examinations should include a biopsy for morphology and an aspirate for local hematology (flow studies are optional). Unsuccessful attempts at bone marrow aspiration/biopsy will not be considered a protocol deviation.

8.1.1.3 Response Evaluation

Objective response will be determined by the investigator at specified timepoints according to the Lugano Response Criteria (Cheson et al. 2014; see Appendix 10).

Endpoints (e.g., ORR, CRR, PFS, EFS) will be calculated programmatically by the Sponsor on the basis of investigator assessments of response at each specified timepoint.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary exams may be performed if clinically indicated.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. As part of the complete physical examination, the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly will be recorded on the appropriate Tumor Assessment eCRF.

A targeted, symptom-directed, physical examinations will include, at a minimum, assessments of the skin, respiratory, cardiovascular systems, and abdomen (liver and spleen), and should be performed at specified postbaseline visits and as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. As part of tumor assessment, targeted physical examination should also include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, splenomegaly, or other findings of concern for lymphoma which will be recorded on the appropriate Tumor Assessment eCRF.

8.2.2 Vital Signs

Vital signs will be assessed with a completely automated device while the participant is in a seated or semi-supine position after 5 minutes of rest and will include temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure. Manual techniques will be used only if an automated device is not available.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS interval, QT interval, and QT interval corrected through use of Fridericia's formula (QTcF)/QT interval.

All ECG recordings must be performed through use of a standard high-quality, high-fidelity digital electrocardiograph machine. Lead placement should be as consistent as possible. The ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. The following should be recorded on the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

8.2.4 Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment
  - Note: For oncology trials, certain abnormal values may not qualify as adverse events.

Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 2 months after the last dose of mosunetuzumab, 3 months after the last dose of tiragolumab, and 5 months after the last dose of atezolizumab should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified. This is not required if the patient has discontinued study treatment and started a new treatment regimen.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the schedule of activities.

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report (CSR).

8.2.5 Unscheduled Visits

Unscheduled visits may be performed if clinically indicated. Participants will undergo the specified assessments, and additional assessments may be performed if clinically indicated, as determined by the investigator.

8.2.6 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 90 days after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit an updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports will be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Mosunetuzumab	*Mosunetuzumab* Investigator's Brochure
Tiragolumab	*Tiragolumab* Investigator's Brochure
Atezolizumab	*Atezolizumab* Investigator's Brochure
Tocilizumab	*Tocilizumab* Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the associated study drug's Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of mosunetuzumab, 3 months after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, and 3 months after the final dose of tocilizumab.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 3 months after the final dose of tiragolumab and 2 months after the final dose of tocilizumab.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.7)
- Suspected transmission of an infectious agent by a study treatment, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

Adverse Events of Special Interest Specific to Mosunetuzumab

- Grade ≥2 CRS
- Grade ≥2 neurologic adverse event
- Grade ≥2 injection-site reaction
- Any suspected HLH or macrophage activation syndrome (MAS)
- TLS (minimum Grade 3 by definition)
- Febrile neutropenia (minimum Grade 3 by definition)
- Grade ≥2 AST, ALT, or total bilirubin elevation
- Any Grade disseminated intravascular coagulation (minimum Grade 2 by definition)

- Grade ≥2 tumor flare (e.g., manifestation of signs/symptoms associated with an increase in size of known nodal or extranodal lesions by clinical or radiographic assessment, new onset or worsening of preexisting pleural effusions)
- Any Grade pneumonitis/interstitial lung disease (excluding pneumonia of infectious etiology)

Adverse Events of Special Interest Specific to Atezolizumab and Tiragolumab

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, CRS, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

8.3.9 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, *access to the* Medical *Monitors is* available 24 hours per day, 7 days per week. *Details will be provided separately.*

8.4 PHARMACOKINETICS

Serum samples will be collected for measurement of serum concentrations of mosunetuzumab, tiragolumab, and atezolizumab as specified in the schedule of activities (see Section 1.3). Predose serum rituximab or obinutuzumab PK samples are required in order to characterize any potential interactions between rituximab or obinutuzumab PK and the clinical effects of mosunetuzumab.

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of mosunetuzumab, tiragolumab, and atezolizumab. Samples collected for analyses of mosunetuzumab, tiragolumab, and atezolizumab serum concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Also, these data *may* be used to understand the relationship of PK exposure to dose and support characterization of dose/exposure–response relationships in the combination setting. In addition, these data *may* be used to explore and characterize the potential PK interactions between tiragolumab, atezolizumab, and mosunetuzumab.

PK samples will be destroyed no later than 5 years after the final CSR has been completed to allow for assay development and validation (if needed).

8.5 PHARMACODYNAMICS

See Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

Genetic biomarker assessments will not be performed in this study.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Blood, PBMC, and plasma samples for exploratory research on biomarkers and biomarker assay development
- Newly collected (or archival) tumor tissue sample obtained at baseline for exploratory research on biomarkers and biomarker assay development
  - A representative formalin-fixed, paraffin-embedded tumor specimen in a paraffin block (preferred) or 20 slides containing unstained, serial sections must be submitted along with an associated pathology report prior to study enrollment.
  - Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50% viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least 3 cores,

embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

- If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if an individual's archival tissue test results do not meet eligibility criteria.

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.10.1.

Exploratory biomarker research may include but will not be limited to RNA-based expression analysis and DNA-based NGS mutation profiling of genes such as *MS4A1* (CD20) or gene signatures associated with tumor immunobiology, lymphocytes, activation status, and phenotypes of immune cells, cytokines associated with T-cell activation, CRS, and neurotoxicity.

Screening plasma, blood, and tumor tissue samples, including those collected from individuals who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 2 and Table 3). Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.10.2) biomarker samples will be destroyed no later than 5 years after the final CSR has been completed.

For enrolled participants, remaining archival tissue blocks will be returned to the site upon request or no later than the date of final closure of the clinical database, whichever occurs first. For individuals who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

Data generated from samples collected for exploratory biomarker research will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants. In addition, given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or participants unless required by law. The aggregate results of any conducted research

will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Antibodies to mosunetuzumab, tiragolumab, or atezolizumab will be evaluated in serum samples collected from all participants according to the schedule of assessments. Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee. Antibodies to tocilizumab will be measured in serum samples from participants who receive tocilizumab during the study as specified in Appendix 8.

Serum samples will be screened for antibodies binding to mosunetuzumab, tiragolumab, or atezolizumab, and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to mosunetuzumab, tiragolumab, or atezolizumab and/or further characterize the immunogenicity of mosunetuzumab, tiragolumab, or atezolizumab.

The detection and characterization of antibodies to mosunetuzumab, tiragolumab, or atezolizumab will be performed through use of three validated assay methods by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for mosunetuzumab, tiragolumab, or atezolizumab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment. Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to mosunetuzumab, tiragolumab, or atezolizumab.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.10.1 Tumor Biopsies (Participants Providing Separate Consent)

Consenting participants in Expansion Cohort C, Cohort D, and Cohort F may undergo optional paired tumor biopsies at baseline and between C1D15–C2D1 (if the first dose of tiragolumab is given during Cycle 1) or C2D15 (if the first dose of tiragolumab is given during Cycle 2) study treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by

the investigator). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

The Informed Consent Form will contain a separate section that addresses optional biopsies. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of undergoing optional biopsies. Participants will be told that they are free to choose not to undergo optional biopsies and may withdraw their consent at any time and for any reason. A separate, specific signature will be required to document a participant's agreement to undergo optional biopsies. Participants who choose not to undergo optional biopsies will not provide a separate signature. The investigator should document whether or not the participant has given consent to undergo optional biopsies and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

Samples may be used for exploratory biomarker research as described in Section 8.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. See Section 8.7 for information on duration of sample storage and availability of data from biomarker analyses.

8.10.2 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.10.2.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides).
The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. The RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.10.2.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10) will not be applicable at that site.

8.10.2.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including but not limited to research on biomarkers related to mosunetuzumab, tiragolumab, atezolizumab, or their targets, diseases, or drug safety:

- Blood samples collected at baseline
- Leftover blood, serum, plasma, PBMC, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. Whole genome sequencing and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which participants are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.10.2.4 Data Protection, Use, and Sharing

The RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual participant basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.10.2.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period.
A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and

(if applicable) the date(s) of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.10.2.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.10.2.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study.

9.2 SAMPLE SIZE DETERMINATION

The sample size for the Phase Ib dose-finding portion of the study is based on the dose-determining rules described in Section 4.3.4. The planned enrollment for the Safety Run-In Cohorts A, B, and E is approximately 6–18 participants. After the dose

has been determined for mosunetuzumab in combination with tiragolumab, approximately 80 participants will be enrolled in the Phase II single-arm expansion portion of the study (40 participants with R/R DLBCL in Cohort E and 40 participants with R/R FL in Cohort F). Additionally, approximately 20 participants will be enrolled in the Phase II single-arm expansion portion with atezolizumab (Cohort F).

The primary efficacy endpoint is best ORR (CR or PR) in the study, as determined by the investigator with the use of Lugano 2014 criteria (Appendix 10).

With 20 or 40 participants in a treatment arm, the 95% exact Clopper-Pearson CIs for estimation of the true ORR would have a margin of error not exceeding ±24.3% or ±16.7%, respectively (Clopper and Pearson 1934). Table 8 shows Clopper-Pearson exact 95% CIs corresponding to observed ORR ranging from 30% to 80% based on sample sizes of 20 and 40.

With respect to assessment of safety, point estimates will be presented. Table 9 provides probabilities of seeing at least one adverse event among 20 and 40 participants for true adverse event frequencies ranging from 1%–10%. For example, with 40 participants in a treatment arm, there is at least an 87% chance of observing at least one adverse event with true incidence of ≤5%.

Table 8 Clopper-Pearson Exact 95% Confidence Intervals for Assumed Observed CR Rates based on Sample Size of 20 and 40 Participants

Observed ORR	No. of Participants with OR (95% CI for rate)	
	n=20	n=40
80%	16 (56.3%, 94.3%)	32 (64.4%, 90.9%)
70%	14 (45.7%, 88.1%)	28 (53.5%, 83.4%)
60%	12 (36.1%, 80.9%)	24 (43.3%, 75.1%)
50%	10 (27.2%, 72.8%)	20 (33.8%, 66.2%)
40%	8 (19.1%, 63.9%)	16 (24.9%, 56.7%)
30%	6 (11.9%, 54.3%)	12 (16.6%, 46.5%)

CR=complete response; OR=odds ratio; ORR=objective response rate.

Table 9 Probabilities of Observing Adverse Events with Different Underlying Incidences based on Sample Size of 20 and 40 Participants

Underlying Adverse Event Incidence	Probability of Observing the Adverse Event in at least 1 Participant out of	
	n=20	n=40
1.0%	18%	33%
2.5%	40%	64%
5.0%	64%	87%
7.5%	79%	96%
10%	88%	99%

9.3 ANALYSIS SETS

The following populations are defined:

Participant Analysis Set	Description
Evaluable	As defined in Section 4.2.1.
Safety	All participants assigned to study treatment and who take at least one dose of study treatment. Participants will be analyzed according to the treatment they actually received.

9.4 STATISTICAL ANALYSES

9.4.1 General Considerations

The final analysis will be based on participant data collected through study discontinuation. Baseline data are the last data obtained prior to initiation of study treatment. Endpoints are defined in Section 3, Table 4.

In general, data will be summarized as warranted, and listings will be used in place of tables when the samples sizes are small. Continuous variables will be summarized using means, standard deviations, median, and ranges; categorical variables will be summarized using counts and percentages. Summaries will be presented by assigned treatment arm and, if warranted, by dose level.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to the NCI CTCAE v5.0 scale; for CRS, severity will be determined according to ASTCT CRS consensus grading criteria (Appendix 9). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

9.4.2 Primary Endpoint(s)

The primary endpoints are as follows for each study phase:

Phase Ib

- Incidence and severity of adverse events, including DLTs, with severity determined according to NCI CTCAE v5.0; for CRS, severity determined according to ASTCT CRS consensus grading criteria (Appendix 9)

Phase II

- Best ORR, defined as the proportion of participants whose best overall response is a PR or a CR during the study, as determined by the investigator using Lugano 2014 criteria (Appendix 10)

9.4.3 Secondary Endpoints

The secondary endpoints are as follows for each study phase:

Phase Ib

- Best ORR (CR or PR at any time) in the study as determined by the investigator using Lugano 2014 criteria (Appendix 10)
- Best CR rate, defined as the proportion of participants whose best overall response is a complete response during the study, as determined by the investigator using Lugano 2014 criteria (Appendix 10)
- DOR, defined as the time from the first occurrence of a documented objective response (CR or PR) to disease progression or relapse, as determined by the investigator using Lugano 2014 criteria (Appendix 10), or death from any cause, whichever occurs first

Phase II

- Best CR rate on study as determined by the investigator using Lugano 2014 criteria (Appendix 10)
- DOR, defined as the time from the first occurrence of a documented objective response (CR or PR) to disease progression or relapse, as determined by the investigator using Lugano 2014 criteria (Appendix 10), or death from any cause, whichever occurs first
- PFS, defined as the time from the first study treatment to the first occurrence of disease progression or relapse, as determined by the investigator using Lugano 2014 criteria (Appendix 10), or death from any cause, whichever occurs first
- EFS, defined as the time from the first study treatment to the first occurrence of disease progression or relapse, as determined by the investigator using Lugano 2014 criteria (Appendix 10), initiation of new anti-lymphoma treatment, or death from any cause, whichever occurs first
- OS, defined as the time from the first study treatment to death from any cause

- Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v5.0; for CRS, severity determined according to the ASTCT CRS Consensus Grading criteria (Appendix 9)

Phase Ib and Phase II

- C_{max}
- C_{min}
- Total exposure (AUC), CL, and volume of distribution, as estimated by population-PK modeling, as appropriate, and supported by data

9.4.4 Exploratory Endpoints

The exploratory efficacy endpoint is best ORR (CR or PR at any time) in the study as determined by automated response using Lugano 2014 criteria (aLugano), a deep learning algorithm. Analysis of aLugano will be perfomed on the PET/CT–evaluable populations, defined as all participants with available PET/CT scans at baseline and during treatment.

Automated total metabolic tumor volume (aTMTV), an exploratory imaging biomarker, will be calculated using a deep learning algorithm on the evaluable population of participants with PET/CT scans available at baseline.

Additional analyses of aLugano, aTMTV, and other exploratory biomarkers may be performed in the context of this study and in aggregate with data from other studies.

9.4.5 Other Analyses

9.4.5.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm and dose level. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm and dose level.

9.4.5.2 Summaries of Treatment Group Comparability/Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, sex, race/ethnicity, duration of malignancy, and baseline ECOG PS) will be summarized by treatment arm and dose level.

9.4.5.3 Pharmacokinetic Analyses

Individual and mean serum concentrations of mosunetuzumab, tiragolumab, and atezolizumab versus time data will be tabulated and plotted by dose level. The C_{max} and C_{min} of mosunetuzumab, tiragolumab, and atezolizumab will be summarized.

Additional PK analyses will be conducted as appropriate.

9.4.5.4 Immunogenicity Analyses

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, participants are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA-positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Participants are considered to be ADA negative if they are ADA negative or have missing data at baseline, and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

9.5 INTERIM ANALYSES

9.5.1 Planned Interim Safety Analyses

The IMC will review all cumulative safety data by cohort and by treatment arm during the Phase II expansion portion of the study, occurring when approximately 20 and 40 total participants in the Phase II Expansion Cohorts of each treatment arm have each received at least 2 cycles of treatment, or more frequently as indicated or requested by the Medical Monitor. The IMC may make recommendations regarding study conduct, including but not limited to the following: performing additional safety analyses, amending the study protocol, holding participant enrollment pending further safety evaluations, holding or discontinuing study treatment, making decisions to modify or discontinue the requirement for hospitalization with study treatment, or terminating the study. Moreover, safety data will also be reviewed as part of the interim efficacy analysis of 20 patients enrolled in Expansion Cohort C (Section 9.5.2), which will determine whether Safety Run-In Cohort E may be opened for enrollment. This decision will be based on the recommendation from the IMC upon evaluation of both safety and efficacy data for Cohorts A (or B) and C. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRB/EC. A detailed plan will be included in the IMC Charter.

In addition to the periodic safety data reviews, ongoing safety monitoring will be performed to guide potential early stopping of enrollment in the event of unacceptable toxicity in any given arm or a lower-than-expected response rate in the arms. Safety stopping rules for all treatment-related Grade 5 adverse events (excluding from disease progression), Grade ≥ 3 immune-mediated adverse events, and Grade ≥ 3 treatment-related serious adverse events will be implemented for each arm. If the safety stopping rules are above the threshold for that arm, the Sponsor will stop enrollment in that arm. For each arm, enrollment in that specific arm will be stopped if, at the time of an interim analysis, the incidence of treatment-related Grade 5 adverse events (excluding from disease progression) is $\geq 10\%$ in that arm, if the incidence of Grade ≥ 3

immune-mediated adverse events (as defined in the list of "Adverse Events of Special Interest Specific to Atezolizumab and Tiragolumab" in Section 8.3.8) is >25%, or if the incidence of Grade ≥3 serious adverse events related to study treatment is >50%. For each arm, the safety stopping rules for treatment-related Grade 5 adverse events, Grade ≥3 treatment-related serious adverse events, and Grade ≥3 immune-mediated adverse events are based on absolute incidences and not on probabilities.

9.5.2 Interim Efficacy Analyses

Interim analyses will be conducted for futility in expansion Cohorts C and D. Specifically, for each expansion cohort, after approximately 20 patients have completed their first tumor assessment at the recommended expansion dose regimen either as part of a safety run-in cohort or the expansion cohort, an interim analysis will be conducted to inform potential early stopping of enrollment if observed response rates are lower than expected. The interim analysis of 20 patients enrolled in Expansion Cohort C will determine whether Safety Run-In Cohort E may be opened for enrollment. This decision will be based on the recommendation from the IMC upon evaluation of both safety and efficacy data for Cohorts A (or B) and C. Using the posterior probability approach with non-informative prior, if 14 of 20 or fewer patients respond to treatment in expansion Cohort C, there will be a 90% chance that the true ORR is ≤84%. If 6 of 20 or fewer patients respond to treatment in expansion Cohort D, there will be a 90% chance that the true ORR is ≤46%. In this case, enrollment in the cohorts may be stopped.

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel, who will have full access to unblinded data. Access to treatment assignment information will follow the Sponsor's standard procedures.

9.6 INDEPENDENT DATA MONITORING COMMITTEE

There is no independent Data Monitoring Committee for this study.

10. REFERENCES

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

TABLE OF CONTENTS

A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, *Clinical Trials Directive (2001/20/EC)* or *Clinical Trials* Regulation 536/2014 (*European Economic Area* sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 4.7).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant.

A participant who is re-screened is not required to sign another Informed Consent Form if the re-screening occurs within 28 days from the previous Informed Consent Form signature date.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also

be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 30 sites globally will participate to enroll approximately 6–118 participants. Enrollment will occur after approval by the Sponsor, and the dose group and patient number assignment will be done by an interactive voice or web-based response system (IxRS).

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker, and pharmacokinetic analyses), as specified in Section 8 and Appendix 2. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Radiographic images may be submitted to an Independent Review Facility for a quality and completeness check, for potential review, and for temporary storage prior to transferring images to the Sponsor.

An Internal Monitoring Committee will monitor and evaluate participant safety through the duration of the study (see Section 4.8).

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/*or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including but not limited to Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written

approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the Case Report Form (CRF) or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly

inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, absolute neutrophil count, absolute lymphocyte count, and other cells • Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, magnesium, total and direct bilirubin, albumin, ALP, ALT, AST, gamma-glutamyl transpeptidase, and uric acid • Lactate dehydrogenase • C-reactive protein, serum ferritin • For atezolizumab-treated participants only: Serum amylase and lipase • Coagulation: INR or PT, aPTT, and fibrinogen (fibrinogen will be collected when monitoring HLH and/or severe CRS events) • Thyroid function testing: thyroid-stimulating hormone and free T4 • Quantitative immunoglobulins: IgA, IgG, and IgM • HIV serology • HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test • HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test • EBV and CMV serology by quantitative PCR using peripheral blood samples – Notes: If local laboratory assessments are not available for quantitative PCR detection of active EBV and CMV, then samples may be analyzed at a central laboratory • Pregnancy test – All women of childbearing potential will have a serum pregnancy test at screening (within 14 days prior to Cycle 1, Day 1). Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

CMV = cytomegalovirus; CRS = cytokine release syndrome; EBV = Epstein-Barr virus; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HLH = hemophagocytic lymphohistiocytosis.

Investigators must document their review of each laboratory safety report.

Appendix 3
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication
  - Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition

- Medical or surgical procedure (e.g., endoscopy, appendectomy)
  - The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.
  - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.
- Results in persistent disability or incapacity
  - The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE v5.0 grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE. The severity of cytokine release syndrome (CRS) events will be assessed using ASTCT CRS grading criteria (Lee 2019).

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

For participants receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the

Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information. New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken offline, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF

and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 90 days after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 90 days after the final dose of study treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form, using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the

participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 INFUSION-RELATED/INJECTION REACTIONS

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion/injection should be captured as a diagnosis (e.g., "infusion-related reaction," "injection reaction," or "cytokine release syndrome" on the Adverse Event eCRF). If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated eCRF. If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated eCRF.

A3–7.2 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

For adverse events other than infusion-related/injection reactions (see Section A3–7.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.3 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF

- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.4 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.5 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.6 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.7 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST (>3×ULN) in combination with either an elevated total bilirubin (>2×ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST >3×ULN in combination with total bilirubin >2×ULN
- Treatment-emergent ALT or AST >3×ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.8 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1) that are attributed by the investigator solely to progression of diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). An internal monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.9 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.10 LACK OF EFFICACY OR WORSENING OF LYMPHOMA

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of FL or DLBCL on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of FL or DLBCL"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on 2014 Lugano Response Criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A3–7.11 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care

- Planned hospitalization required by the protocol (e.g., prophylactic hospitalization prior to mosunetuzumab dosing according to risk or prior occurrence of CRS)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition.
  - The participant has not experienced an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.12 CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
  - In some cases, a medication error may be intercepted prior to administration of the drug.

Note: Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). For mosunetuzumab, tiragolumab, atezolizumab, and tocilizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

In addition, all special situations associated with mosunetuzumab, tiragolumab, atezolizumab, and tocilizumab regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

A3–7.13 SAFETY BIOMARKER DATA

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

Appendix 4
Contraceptive and Barrier Guidance

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A4–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of mosunetuzumab, 3 months after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, and 3 months after the final dose of tocilizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A4–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 3 months after the final dose of tiragolumab and 2 months after the final dose of tocilizumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects

on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A4–3 ABORTIONS

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A4–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 5
Genetics: Use and Analysis of DNA

Genetic biomarker assessments will not be performed in this study.

Appendix 6
Safety Plan: Management of Identified and Potential Risks

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A6–1 RISKS ASSOCIATED WITH STUDY DRUGS

Mosunetuzumab and tiragolumab are not approved and clinical development is ongoing. Atezolizumab has been approved in some countries for the treatment of urothelial carcinoma, non-small cell lung cancer, small cell lung cancer, and hepatocellular carcinoma. Refer to local prescribing information for further details of approved use of atezolizumab. The safety plan for participants in this study is based on clinical experience with mosunetuzumab, tiragolumab, and atezolizumab in completed and ongoing studies. The anticipated safety risks for mosunetuzumab, tiragolumab, and atezolizumab are outlined below. Please refer to the Mosunetuzumab, Tiragolumab, and Atezolizumab Investigator's Brochures for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants. Eligibility criteria have been designed to exclude individuals at higher risk for toxicities.
As described in Section 4.1, enrollment will be staggered such that the first 3 participants in a Safety Run-In Cohort will have respective Cycle 1 Day 1 treatments administered ≥72 hours apart. Enrollment of subsequent participants in the same cohort will be staggered such that their Cycle 1 Day 1 treatments are administered ≥24 hours apart. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dose modification and treatment interruption or discontinuation, are provided below.

A6–1.1 MOSUNETUZUMAB

Identified Risks with Mosunetuzumab

On the basis of clinical data to date with mosunetuzumab, the following identified risks are described below. Refer to the Mosunetuzumab Investigator's Brochure for a description of all anticipated risks for mosunetuzumab.

A6–1.1.1 Cytokine Release Syndrome

The mechanism of action of mosunetuzumab is immune cell activation against CD20-expressing cells; therefore, a spectrum of events involving infusion-related reactions (IRRs), target-mediated cytokine release, and/or hypersensitivity with or without emergent ADAs, may occur. Other CD20-directed therapies and immunomodulatory therapies have been associated with IRRs, cytokine release syndrome (CRS), and/or hypersensitivity (Rituxan® United States Prescribing Information [USPI]; Gazyva® USPI; Blincyto® USPI).

CRS following mosunetuzumab administration has been reported in clinical trials of mosunetuzumab. See the current Mosunetuzumab Investigator's Brochure for clinical details.

To date, CRS events observed with mosunetuzumab have been mostly mild to moderate in severity and include symptoms such as fever, headache, and myalgia, and respond to symptomatic treatment with analgesics, anti-pyretics, and antihistamines as indicated.

Severe or life-threatening presentations of CRS, such as hypotension, tachycardia, dyspnea, or chest discomfort, should be treated aggressively with supportive and resuscitative measures as indicated, including the use of tocilizumab and/or high-dose corticosteroids, IV fluids, and other supportive measures per institutional practice. Severe CRS may be associated with other clinical sequelae such as disseminated intravascular coagulation, capillary leak syndrome, or may manifest as hemophagocytic lymphohistiocytosis (HLH). Standard of care for severe or life-threatening CRS resulting from immune-based monoclonal antibody therapy has not been established; case reports and recommendations for CD19 chimeric antigen receptor (CAR) T have been published (Teachey et al. 2013; Lee et al. 2014, Maude et al. 2014; Neelapu et al. 2018; also see FDA approval for three products describing risk management for CRS [Yescarta® USPI; Kymriah® USPI; Tecartus® USPI]).

Disease-related factors that may be associated with an increased risk of severe CRS following CAR T cell therapy, and therefore, potentially other T-cell engaging therapies, include but are not limited to lymphoma bone marrow involvement, extranodal disease, B-cell lymphocytosis, and the presence of circulating peripheral malignant cells. Regarding participants with the above disease-related factors, the Medical Monitor should be consulted; additional monitoring (i.e., more frequent measurements of vital signs) during mosunetuzumab dosing (especially first dose) should be undertaken and management of treatment-emergent adverse events (including CRS) must adhere to guidance in Section A6–1.

To minimize the risk and sequelae of CRS, corticosteroid premedication should be administered as described in Section 6.1.1.

Refer to Appendix 3 for adverse event reporting procedures related to CRS. See Appendix 9 for the CRS Grading Scale. See Appendix 7 for anaphylaxis management.

Management guidelines for CRS are described in Section A6-2.3.1.

A6–1.1.2 Neutropenia

Neutropenia is a known class effect associated with other CD20-directed therapies as well as blinatumomab and is a known risk for mosunetuzumab (Blincyto USPI). Reversible neutropenia has been observed following mosunetuzumab treatment in Study GO29781. Some participants developing neutropenia have received growth factor support and/or temporary treatment holds. Refer to the Mosunetuzumab Investigator's Brochure for details.

Management guidelines for neutropenia are described in Section A6-2.3.2.

A6–1.1.3 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a known pharmacodynamic effect of anti-tumor therapy in hematologic malignancies including non-Hodgkin lymphoma (NHL). Tumor lysis syndrome has been reported with blinatumomab, CAR T–cell therapy, and other CD20 directed therapy (Blincyto USPI; Gazyva USPI; Rituxan USPI; Porter et al. 2011). The inherent risk of TLS is dependent on the malignancy being treated and individual participant characteristics (Coiffier et al. 2008). There is the identified risk of TLS if treatment with mosunetuzumab results in the rapid destruction of a large number of tumor cells.

The risk of TLS with mosunetuzumab in NHL participants is predicted to be highest for those with bulky disease (defined in the context of TLS as any lesion ≥ 10 cm on the screening computed tomography [CT] scan) and elevated pretreatment lactate dehydrogenase (LDH) levels, particularly in the presence of dehydration or compromised renal function. While diffuse large B-cell lymphoma, transformed lymphomas, and mantle cell lymphomas may be at higher risk of TLS as compared with follicular, marginal, and small cell lymphomas, any risk stratification based on tumor type must be considered along with the effectiveness of therapy (Cairo et al. 2010; Howard et al. 2011).

Management guidelines for TLS including prophylactic measures are described in Section A6–2.3.6.

A6–1.1.4 Infections

Infections are an identified risk following mosunetuzumab treatment. Infections have been reported in participants receiving other CD20-directed therapies as well as blinatumomab (Blincyto USPI; Gazyva USPI; Rituxan USPI). Therefore, mosunetuzumab should not be administered in the presence of active severe infections. Investigators should exercise caution when considering the use of mosunetuzumab in participants with history of recurring or chronic infections or with underlying conditions that may predispose participants to infections (Section A6–2.3.7).

Hepatitis B reactivation has been reported with other CD20-directed therapies (Law et al. 2016). Patients with positive test results for active hepatitis B virus (HBV) infection defined by hepatitis B surface antigen (HBsAg) or positive total hepatitis B core antibody (HBcAb) with positive HBV PCR, or patients with hepatitis C virus (HCV) infection as assessed by PCR, will be excluded from this study *(see Section 5.2)*. Patients with occult or prior HBV infection (defined as negative HBsAg and positive HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing on Day 1 of every cycle and every 3 months for at least 12 months after the last cycle of study treatment and appropriate antiviral therapy (Hwang et al. 2020). Participants who experience hepatitis B reactivation should start

antiviral therapy (if not already initiated). Participants with rising viral load on appropriate antiviral therapy should consider study treatment discontinuation if in the investigator's opinion the benefit–risk profile of continued treatment is unfavorable. Participants who demonstrate evidence of hepatitis reactivation should be evaluated and continuation of mosunetuzumab therapy guided by benefit–risk assessment.

Preexisting chronic active Epstein-Barr virus (EBV) infection may be a risk factor for developing secondary HLH following mosunetuzumab administration. Patients with chronic active EBV should not receive mosunetuzumab.

Patients with HIV infection will be excluded from participation in the study because signs and symptoms of HIV may confound assessment of the safety profile of mosunetuzumab. HIV has also been associated with development of secondary HLH. Patients with HIV and known or suspected chronic active EBV infection will be excluded from this trial due to the risk of secondary HLH (see Section 5.2).

Management guidelines for infections are described in Section A6–2.3.7.

A6–1.1.5 Tumor Flare

Adverse events associated with tumor flare have been reported *with T cell–engaging therapies and are* consistent with the mechanism of action *leading* to influx of T cells into tumor sites. *Events involving tumor flare have been reported in Study GO29781. These* events *tend* to *occur with* a short time to onset following *mosunetuzumab administration and present with varying degrees of severity.* In addition, depending on tumor size and anatomic location, tumor flare may potentially result in mass effects on vital structures including airways, major blood vessels, gastrointestinal tract (risk of perforation and hemorrhage), and/or major organs.

Depending on the nature of the tumor flare, further medical and/or surgical management may be necessary. If such manifestations are associated with mosunetuzumab, the investigator should consider those events to be tumor flare and report as "tumor flare."

Management guidelines for tumor flare/inflammation are described in Section A6–2.3.10. *See the most recent Mosunetuzumab Investigator Brochure for most updated information on tumor flare.*

A6–1.1.6 Injection Site Reactions

Localized injection site reactions following SC administration of the anti-CD20 monoclonal antibody rituximab have been observed (Assouline et al. 2016). Most of these were mild to moderate in severity (MabThera® E.U. Summary of Product Characteristics [SmPC]). As CD4+ and CD8+ T cells as well as B cells reside in the skin, localized reactions following mosunetuzumab SC administration may occur and

mild injection site reactions have been observed in participants treated with mosunetuzumab SC in Study GO29781 (Mueller et al. 2014; Egbuniwe et al. 2015).

See Appendix 3 for adverse event reporting procedures related to injection site reactions.

Management guidelines for injection site reactions are described in Section A6–2.3.4.

Potential Risks associated with Mosunetuzumab

The clinical risks associated with mosunetuzumab are not fully known at this time. This section summarizes the potential risks of treatment with mosunetuzumab. The risks described below are based on the clinical observation from a total of 720 participants exposed to mosunetuzumab in five ongoing clinical studies with mosunetuzumab, the anticipated mechanism of action, clinical experience from molecules of the same class and results from nonclinical studies.

A6–1.1.7 Hemophagocytic Lymphohistiocytosis

CRS with features of adult-onset secondary or reactive macrophage activation syndrome (MAS)/HLH has been reported with blinatumomab as well as CAR adoptive T-cell therapy (Blincyto USPI; Teachey et al. 2013; Lee et al. 2014). A fatal case of secondary HLH, in a participant with evidence of chronic active EBV infection (positive for EBV as assessed by EBV-encoded small RNA in situ hybridization), has been reported in Study GO29781 (refer to the current Mosunetuzumab Investigator's Brochure for details).

While severe CRS and secondary HLH have overlapping presentation and symptoms, secondary HLH may be precipitated by other conditions including infections, autoimmune disease and malignancies (Ramos-Casals 2014). The prevalence of these conditions in the study participant population makes the distinction between severe CRS and HLH and identification of inciting factors challenging. For example, in one case series, B-cell malignancies were the most common malignancy associated with reactive HLH (Rivière et al. 2014). Furthermore, active infection with EBV is one of the most common infectious causes of HLH, while reactivation of latent EBV may occur in participants with chronic lymphocytic leukemia (CLL), which in turn may lead to HLH (Rath et al. 2008; Lim et al. 2014; Hashemi-Sadraei et al. 2015; Schram and Berliner 2015). It remains unknown whether mosunetuzumab treatment may further increase the risk of developing HLH in participants who have additional risk factors.

Management guidelines for HLH are described in Section A6–2.3.3.

A6–1.1.8 Neurologic Adverse Events

Encephalopathy has been observed in in the setting of CRS and/or elevation in liver function tests (LFTs) following mosunetuzumab treatment (refer to the Mosunetuzumab Investigator's Brochure for details).

Neurologic toxicity has been reported in cynomolgus monkeys administered mosunetuzumab (refer to Mosunetuzumab Investigator's Brochure for details) and was frequently reported in participants treated with blinatumomab and CD19 CAR T–cell therapy (Blincyto USPI; Kochenderfer et al. 2014; Maude et al. 2014). Reported symptoms in participants treated with blinatumomab or CAR T–cell therapy have included headache, confusion, aphasia, encephalopathy, tremor, seizure, and other neurologic events. The etiology of toxicity in these settings is uncertain and may not be responsive to cytokine-directed therapy such as tocilizumab but has generally improved with treatment discontinuations and corticosteroids (Blincyto USPI; Viardot et al. 2010; Kochenderfer et al. 2014). Encephalopathy was observed in the setting of CRS and/or elevation in LFTs following mosunetuzumab treatment. Based on available clinical data, neurologic adverse events observed with mosunetuzumab have been mild in severity with early onset. The most frequent neurologic events include headache, dizziness, and insomnia (refer to the Mosunetuzumab Investigator's Brochure for details).

Management guidelines for neurologic adverse events are described in Section A6–2.3.5.

A6–1.1.9 Thrombocytopenia

Thrombocytopenia is associated with other CD20-directed therapies as well as blinatumomab (Blincyto USPI). Reversible thrombocytopenia has been observed following mosunetuzumab treatment in Study GO29781. Refer to the Mosunetuzumab Investigator's Brochure for details.

In nonclinical testing of mosunetuzumab in cynomolgus monkeys, hematology findings included transiently decreased WBC, lymphocyte, monocyte, eosinophil, basophil, and platelet counts within the first day of mosunetuzumab exposure, followed by recovery or rebound recovery between Days 4–8. See the Mosunetuzumab Investigator's Brochure for further details on nonclinical assessments on mosunetuzumab.

Management guidelines for thrombocytopenia are described in Section A6–2.3.8.

A6–1.1.10 Elevated Liver Enzymes

Transient Grade 3 AST elevation in the setting of Grade 2 CRS as well as Grade 3 hepatic encephalopathy or Grade 4 elevation in LFTs have been observed following mosunetuzumab treatment (refer to the Mosunetuzumab Investigator's Brochure for details).

In nonclinical testing with mosunetuzumab in cynomolgus monkeys, dose-dependent increases in serum total bilirubin along with CRP, fibrinogen, PT, and aPTT were observed, consistent with mosunetuzumab-induced cytokine release and an acute-phase protein response, with minimal activation of the coagulation system. Possible drug-related microscopic findings in the liver included single-cell hepatocyte degeneration or necrosis and immune cell infiltration in the portal area. All findings showed evidence of reversibility. See the Mosunetuzumab Investigator's Brochure for further details on nonclinical assessments on mosunetuzumab.

Participants with elevated LFTs at screening will be excluded from this trial (see Section 5.2).

Management guidelines for elevated liver enzymes are described in Section A6–2.3.9.

A6–1.1.11 Immunogenicity (Anti-Drug Antibodies)

As with any recombinant antibody, mosunetuzumab may elicit an immune response and participants may develop antibodies against the molecule, which may have an impact on the benefit–risk profile of the agent. Therefore, a risk-based strategy will be utilized to detect and characterize ADA responses to mosunetuzumab (Rosenberg and Worobec 2004a, 2004b, 2005; Koren et al. 2008).

A6–1.2 ATEZOLIZUMAB

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions. *In addition,* immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A6–1.2.1 Pulmonary Events

Pulmonary events may present as new or worsening cough, *chest pain, fever, dyspnea,* fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Participants will be assessed for pulmonary signs and symptoms throughout the study and will also have CT scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. *Coronavirus disease 2019 (COVID-19) evaluation should be performed per institutional guidelines where relevant.*

Management guidelines for pulmonary events are described in Section A6–2.3.11.

A6–1.2.2 Hepatic Events

Participants eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment.

Management guidelines for hepatic events are described in Section A6–2.3.9.

A6–1.2.3 Gastrointestinal Events

Management guidelines for diarrhea or colitis are described in Section A6–2.3.12.

A6–1.2.4 Endocrine Events

Management guidelines for endocrine events are described in Section A6–2.3.13.

A6–1.2.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events).
Management guidelines for ocular events are described in Section A6–2.3.14.

A6–1.2.6 Pancreatic Events

Management guidelines for pancreatic events are described in Section A6–2.3.15.

A6–1.2.7 Dermatologic Events

The majority of cases of rash *reported with the use of atezolizumab* were mild in severity and self-limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Management guidelines for dermatologic events are described in Section A6–2.3.16.

A6–1.2.8 Neurologic Events

Participants may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies.

Management guidelines for neurologic disorders are described in Section A6–2.3.5.

A6–1.2.9 Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis should be suspected in any participant presenting with signs or symptoms suggestive of meningitis or encephalitis, including but not limited to headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or

electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process. All participants being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Management guidelines for participants with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, are described in Section A6–2.3.17.

A6–1.2.10 Immune-Mediated Cardiac Events

Management guidelines for cardiac events are provided in Section A6–2.3.18.

A6–1.2.11 Immune-Mediated Myocarditis

Immune-mediated myocarditis should be suspected in any participant presenting with signs or symptoms suggestive of myocarditis, including but not limited to laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. *Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on pericardial disorders below) and should be managed accordingly.* Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral [e.g., in a participant who reports a recent history of gastrointestinal illness]), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Management guidelines for participants with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, are described in Section A6–2.3.18.

A6–1.2.12 Immune-Mediated Pericardial Disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer-related (metastatic disease or chest radiotherapy), cardiac injury–related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Section A6–2.3.18. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

A6–1.2.13 Renal Events

Eligible participants must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Participants with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the participant to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Management guidelines for participants with signs and symptoms of nephritis, in the absence of an identified alternate etiology, are described in Section A6–2.3.19.

A6–1.2.14 Immune-Mediated Myositis

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography or MRI) features and is confirmed with a muscle biopsy.

Management guidelines for participants with signs and symptoms of myositis, in the absence of an identified alternate etiology, are described in Section A6–2.3.20.

A6–1.2.15 Infusion-Related Reactions

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

Management guidelines for infusion-related reactions and cytokine release syndrome are described in Section A6–2.3.1.

A6–1.2.16 Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to HLH and MAS.

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Management guidelines for HLH are described in Section A6–2.3.3.

A6–1.3 TIRAGOLUMAB

Infusion-related reactions and immune-mediated hepatitis are identified risks with tiragolumab. Lymphopenia is a potential risk with tiragolumab. Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine based inhibition motif domains (TIGIT), tiragolumab is anticipated to enhance T-cell and natural killer (NK)-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to the Tiragolumab Investigator's Brochure for *a detailed description of anticipated* safety *risks for tiragolumab.*

A6–1.3.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic monoclonal antibody (mAb) and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine release may occur. Clinical signs and symptoms include rigors, chills, wheezing, pruritis, flushing, rash, hypotension, hypoxemia, and fever.

IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over 60 minutes followed by a 60-minute observation period. Subsequent infusions and observation times may be shortened if the preceding infusion was well tolerated. All infusions will be administered in an appropriate medical setting.

Management guidelines for IRRs with administration of tiragolumab are described in Section A6–2.3.1.

A6–1.3.2 Immune-Mediated Hepatitis

The use of tiragolumab to block the immune inhibitory receptor TIGIT serves to increase a baseline T-cell and NK-cell immune response, especially in combination with other checkpoint inhibitors (i.e., atezolizumab). A disruption in the functioning of immune checkpoint molecules may lead to imbalances in immunologic tolerance that results in an unchecked immune response, including immune-mediated hepatitis.

See Section A6–2.3.9 *for guidance on the management of immune-mediated hepatitis.*

A6–1.3.3 Immune-Mediated Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT−/−), loss of TIGIT signaling resulted in hyperproliferative T cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT−/− and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT−/− mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutics intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ systems and include but are not limited to colitis, pneumonitis, endocrinopathy, ocular toxicity, pancreatic toxicity, neurologic toxicity, *cardiac toxicity*, nephritis, *myositis,* and *severe cutaneous adverse reactions*.

Participants with a history of autoimmune disease will be excluded from this study. In addition, participants with a history of severe immune-mediated adverse events associated with prior immunotherapy or adverse events that did not resolve to baseline after discontinuation of prior immunotherapy will be excluded from this study (see Section 5.2).

Management guidelines for suspected immune-mediated adverse events are described in Section A6–2.3.

A6–1.3.4 Embryofetal Toxicity

Embryofetal toxicity is a potential risk with tiragolumab. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and CD8+ T cells, and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018). No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies

of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

A6–1.3.5 Lymphopenia

Given the IgG1 backbone of tiragolumab with intact fragment crystallizable (Fc)-effector function, antibody-dependent cell-mediated cytotoxicity (ADCC)–mediated reduction in lymphocyte count is a potential risk.

Lymphopenia is a potential risk with tiragolumab. Transient lymphocyte count decreases without clinical sequelae have been observed in participants treated with tiragolumab with or without atezolizumab. *Participants with a lymphocyte count <500 cells/mL will be excluded from this study (see Section 5.2), and CBCs will be monitored regularly during the study (see Section 1.3).*

A6–1.3.6 Tumor Lysis Syndrome

TLS occurs when tumor cells release their contents into the bloodstream, either spontaneously or in response to therapy, leading to the characteristic findings of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. TLS is a known pharmacodynamic effect of anti-tumor therapy in hematologic malignancies including NHL. The inherent risk of TLS is dependent on the malignancy being treated and individual participant characteristics (Coiffier et al. 2008). There is the potential risk of TLS if treatment with tiragolumab results in the rapid destruction of a large number of tumor cells.

Management guidelines for TLS including prophylactic measures are described in Section A6–2.3.6.

A6–1.4 RISK OF OVERLAPPING TOXICITIES WITH MOSUNETUZUMAB, TIRAGOLUMAB, AND ATEZOLIZUMAB

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential overlapping toxicities in patients treated with tiragolumab plus atezolizumab. Because the expected pharmacological activity of these two molecules is to increase adaptive T-cell immune responses via complementary targets, there is the possibility of heightened immune-mediated responses.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of tiragolumab and atezolizumab, additional immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune check point inhibitors (CPIs) to date has been incorporated into the design and safety management plan (see Section 4.1) in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (see Section 5.2). Patients previously treated with approved or experimental CPI therapy will also be excluded from participation in this study. Owing to the risks of active viral infection and viral reactivation (see Section A6-2.3.7), patients with active infection (including but not limited to HIV, HBV, HCV, EBV, known and/or suspected chronic active EBV infection, or tuberculosis) and/or patients with recent severe infections will be excluded from this study (see Section 5.2).

Because the expected pharmacological activity of both tiragolumab and atezolizumab is to increase adaptive T-cell immune responses that result in pro-inflammatory cytokine production, the potential exists for both agents to aggravate any potential cytokine-mediated toxicity that might be primarily driven by mosunetuzumab. Similarly, given the expected pharmacology of mosunetuzumab includes transient release of pro-inflammatory cytokines, there is potential for mosunetuzumab to exacerbate immune-mediated toxicity associated with tiragolumab and atezolizumab. The following risks are specific areas of potential overlapping toxicity, based on the potential and/or identified risks of each agent: CRS or IRR, HLH, elevated liver enzymes or hepatic events, neurologic adverse events, TLS, and pneumonitis or interstitial lung disease

See Sections A6–2.1 (Dose Modifications) and A6–2.3 (Management Guidelines) in situations where overlapping toxicity is observed.

A6–2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

For all considerations of dose and schedule modifications, the Medical Monitor is available to advise as needed.

General guidelines for mosunetuzumab dose and schedule modifications are described below.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- *Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.*

- *In general, atezolizumab and tiragolumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding atezolizumab and tiragolumab for most Grade 2 toxicities and resume when symptoms and laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.*
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*
- *Hold atezolizumab and tiragolumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab and tiragolumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- *In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab and tiragolumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.*
- *The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab and tiragolumab. Resumption of atezolizumab and tiragolumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab and tiragolumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.*

A6–2.1 DOSE MODIFICATIONS

For Grade 3 CRS, the next mosunetuzumab dose should be reduced, and subsequent doses may be increased if the lower dose was tolerated (see CRS management guidelines in Section A6–2.3.1).

There will be no dose modifications for tiragolumab or atezolizumab.

A6–2.2 TREATMENT INTERRUPTION

Mosunetuzumab, tiragolumab, and atezolizumab (where applicable) dosing will occur only if a participant's clinical assessment and laboratory test values are acceptable. If scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date, with subsequent dosing continuing on a 21-day schedule as applicable.

Study treatment may be delayed as appropriate for management of toxicity. The following guidelines regarding schedule modifications should be followed.

In general participants who experience a Grade 4 non-hematological adverse event related to study treatment should discontinue all study treatment and may not be retreated.

- Because TLS and tumor flare represent pharmacodynamic effects of anti-tumor activity of the study treatment in this trial that may result in clinical benefit, participants who experience Grade 4 TLS or tumor flare may continue study treatment if all toxicities and laboratory abnormalities related to TLS have resolved within 2 weeks. The decision to continue study treatment should be made by the study investigator after discussion with the Medical Monitor. Participants must be hospitalized for TLS prophylaxis and monitoring with the next mosunetuzumab and tiragolumab ± atezolizumab dose.
- Participants who experience Grade 4 CRS may be considered for continued study treatment if the criteria in Table A6–1 are met. The decision to continue study treatment should only be made after consultation between the study investigator and the Medical Monitor.
- Other exceptions may be warranted taking into consideration the benefit–risk ratio for a given individual participant and/or ad-hoc and participant-specific risk mitigations.

Participants who experience an adverse event that either meets the definition of a dose limiting toxicity, a Grade 3 adverse event, or a serious adverse event will be allowed to delay study treatment dosing for up to 21 days in order to recover from the toxicity.

- Consult the Medical Monitor if any dose delays of study treatment during Cycle 1 are being considered.
  - During Cycle 1, study treatment may be administered despite hematologic laboratory abnormalities if no clinically significant symptoms are present; study treatment may be administered for anemia and thrombocytopenia if no transfusions are required.
  - During Cycle 1 of treatment, if a Grade ≥ 3 adverse event, serious adverse event, or adverse event of special interest occurs following C1D1, C1D8, and/or C1D15 dosing, a treatment delay of mosunetuzumab (and tiragolumab and atezolizumab as applicable) up to 7 days and/or modification of the subsequent mosunetuzumab dose may occur at the discretion of the treating investigator physician. In the event that a participant has a toxicity in Cycle 1 necessitating mosunetuzumab interruption for > 7 days, the Medical Monitor should be notified, and the participant may be required to repeat mosunetuzumab at the highest dose previously tolerated prior to resuming the planned treatment schedule.
- For those adverse events that are not considered by the investigator to be attributable to another clearly identifiable cause (e.g., documented disease progression, concomitant medication, or preexisting medical condition), participants may continue to receive additional doses of study treatment, provided that the toxicity has resolved to Grade ≤ 1 within 21 days.

  - For decreased lab values, the abnormality should have resolved to the lower limit of Grade ≤1 or return to ≥80% of the baseline value, whichever is lower.
  - For neutropenia, the ANC should resolve to Grade ≤2 or return to ≥80% of the baseline value, whichever is lower.
  - For increased lab values the abnormality should have resolved to the upper limit of Grade ≤1 or return to ≥120% of the baseline value, whichever is higher.
- Participants who do not fulfill the criteria for dosing after the additional 21 days described in Section A6–2.2 elapse will be discontinued from study treatment and be followed for safety outcomes as described in Section 7.2.
  - Exceptions to this on the basis of ongoing clinical benefit may be allowed following investigator assessment of risk versus benefit and consultation with the Medical Monitor.
  - Exceptions are also allowed for specific adverse events as specified in Section A6–2.3 (e.g., for infections or for immune-mediated adverse events related to tiragolumab or atezolizumab ([see below]).
- For Grade 3 CRS see CRS management guidelines in Section A6–2.3.1.
- For the following findings that occur in the context of Grade ≤2 CRS which lasts <3 days, mosunetuzumab dosing may continue without dose reduction:
  - Grade 3 (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 individual signs and symptoms of CRS
  - Elevation of AST or ALT >3×upper limit of normal (ULN) and/or total bilirubin >2×ULN, with no individual laboratory value exceeding Grade 3
- If a dose delay results in a treatment-free interval of 6 weeks or longer, step-up dosing of mosunetuzumab is required *with 5 mg administered on Day 1 of* the first cycle after the dose delay *before the next planned dose on Day 8. Corticosteroid prophylaxis should be administered on both days to mitigate CRS risks. In the event that a participant has a toxicity necessitating mosunetuzumab interruption for >7 days prior to the C1D8 dose, the participant is required to repeat the 5 mg dose (including the corticosteroid prophylaxis) prior to resuming the planned treatment schedule 7 days after the administration of the 5 mg dose.* Continued treatment with tiragolumab and atezolizumab may continue according to the original cohort schedule.

For adverse events that are considered by the investigator to be attributable to another clearly identifiable cause, participants may continue to receive additional doses of study treatment without the need for dose reductions.

Attribution of a treatment-emergent toxicity to an individual investigational agent may be difficult. Based on the currently known mechanisms of action, mosunetuzumab may cause adverse events similar to but independent of tiragolumab and atezolizumab (e.g., CRS/IRR) and may exacerbate the frequency or severity of tiragolumab or atezolizumab–associated adverse events or may have non-overlapping toxicities with

tiragolumab or atezolizumab. Similarly, tiragolumab and atezolizumab may exacerbate the frequency of adverse events potentially associated with mosunetuzumab.

- Because these scenarios may not always be clinically distinguishable, immune-mediated toxicities should be attributed to all study drugs, unless there is a strong rationale for attribution to a specific drug. Consequently, dose interruptions or treatment discontinuation in response to such adverse events should be applied to all study drugs if causality with one study drug has not been established.
- Resumption of treatment with either mosunetuzumab, tiragolumab, or atezolizumab may be considered in accordance with guidelines described in Section A6–2.3. Such treatment decisions will be made by the treating investigator and if necessary, the Internal Monitoring Committee. The Medical Monitor is available to advise as needed.
- Participants who experience Grade 3 or 4 adverse events that are clearly attributed to mosunetuzumab, tiragolumab, or atezolizumab shall be managed in accordance with adverse event management guidelines described in Appendix 6.
- Tiragolumab and atezolizumab (if applicable) treatment may be temporarily suspended in participants who experience toxicity considered to be related to tiragolumab and atezolizumab (if applicable). Tiragolumab and atezolizumab may be held for a maximum of approximately 12 weeks (or approximately four cycles). If tiragolumab and/or atezolizumab are interrupted for more than approximately 12 weeks for any reason, the participant must permanently discontinue tiragolumab and/or atezolizumab treatment but may continue mosunetuzumab if there is no contraindication and after consultation with the Medical Monitor to determine whether the toxicity is considered related to tiragolumab or atezolizumab and/or to the combination. Continued dosing with single-agent mosunetuzumab will require that all other study eligibility criteria continue to be met.
  - If corticosteroids are initiated for treatment of the toxicity, they must be tapered over $\geq$1 month to the equivalent of $\leq$10 mg/day oral prednisone before tiragolumab and atezolizumab (if applicable) can be resumed.
  - If tiragolumab and atezolizumab (if applicable) are withheld for $>$12 weeks after event onset, the participant will be discontinued from tiragolumab and atezolizumab (if applicable). However, tiragolumab and atezolizumab may be withheld for $>$12 weeks to allow for participants to taper off corticosteroids prior to resuming treatment. Tiragolumab and atezolizumab can be resumed after being withheld for $>$12 weeks if the investigator believes that the participant is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab and tiragolumab should be based on the investigator's benefit–risk assessment and documented by the investigator.* The Medical Monitor is available to advise as needed.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed. The acceptable length of treatment interruption must be based on a benefit–risk assessment by the investigator and in alignment with the protocol

requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

After mosunetuzumab, tiragolumab, and atezolizumab have been permanently discontinued, the participant will be monitored for safety and efficacy as specified in Section 7.2.

A6–2.3 MANAGEMENT GUIDELINES FOR ADVERSE EVENTS ASSOCIATED WITH STUDY TREATMENT

Toxicities associated or possibly associated with tiragolumab or atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of tiragolumab and/or atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance a given participant may be experiencing prior to further administration of tiragolumab or atezolizumab.
In participants who have met the criteria for permanent discontinuation, resumption of tiragolumab and/or atezolizumab may be considered if the participant is deriving benefit and has fully recovered from the immune-mediated event. The decision to re-challenge patients with tiragolumab and/or atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A6–2.3.1 Cytokine Release Syndrome and Infusion-Related Reactions

See Section 6.1.1 for premedication requirements with corticosteroids prior to treatment with mosunetuzumab.

No premedication is indicated for the administration of tiragolumab or atezolizumab. However, participants who experience an infusion-related reaction (IRR) or cytokine release syndrome (CRS) with tiragolumab or atezolizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Management guidelines for CRS or IRR following study treatment are summarized in Table A6–1 with the grading of CRS following American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria described in Appendix 9

(Lee 2019). An IRR towards tiragolumab or atezolizumab may be indistinguishable from CRS; hence, their evaluation and treatment are identical.

As participants may have received corticosteroid premedication, a fever response may be blunted. Therefore, adverse events attributed to mosunetuzumab consistent with a diagnosis of CRS, and associated with fever, hypotension, or hypoxia not attributable to any other cause, should be recorded as CRS. CRS events that manifest with hypotension and/or hypoxia but with no fever should be graded depending on management required for hypotension and/or hypoxia. These types of events correspond to minimum ASTCT Grade 2. Other adverse events occurring within 24 hours after mosunetuzumab administration should be reported as individual adverse events (e.g., headache or chills).

Management of Grade ≥3 CRS should be immediately discussed between the treating investigator and the Medical Monitor. As noted in Table A6–1, even moderate presentations of CRS in participants with extensive comorbidities should be monitored closely with consideration given to ICU admission and tocilizumab administration.

Severe SARS-CoV-2 infection is associated with a dysregulated immune response involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ. If a trial participant develops severe CRS, the differential diagnosis should include SARS-CoV-2 and relevant testing performed at the discretion of the investigator. If a diagnosis of SARS-CoV-2 infection is confirmed, study treatment should be interrupted, and the disease should be managed as per local or institutional guidelines.

Attribution of an IRR/CRS event to either mosunetuzumab, tiragolumab, or atezolizumab may not be possible depending on the timing of the IRR/CRS event. Consequently, for participants who experience IRR or CRS events, management, including any modifications to dosing in subsequent cycles, will follow the following general guidelines.

A6–2.3.1.1 Grade 3 CRS Events

Participants who experience a Grade 3 CRS event should be managed according to the guidance in Table A6–1. The next dose of mosunetuzumab should be reduced as described in Table A6–1. The Medical Monitor should be informed and may advise on the approach.

Participants who have received mosunetuzumab monotherapy in Cycle 1 and who experience a Grade 3 CRS event in Cycle 1, may proceed to receive combination treatment with tiragolumab ± atezolizumab in Cycle 2 and beyond at the discretion of the investigator and after a careful benefit–risk assessment. If the CRS event occurs after the initiation of tiragolumab and/or atezolizumab, tiragolumab and atezolizumab (if applicable) should generally be discontinued, but participants may proceed to receive combination treatment with tiragolumab ± atezolizumab in Cycle 2 and beyond at the discretion of the investigator after a careful benefit–risk assessment. There will be no

dose reductions for tiragolumab or atezolizumab. If Grade 3 CRS recurs with subsequent doses, consider permanent discontinuation of all study treatment.

A6–2.3.1.2 Grade 4 CRS Events

All participants who experience a Grade 4 CRS event should be managed according to the guidance in Table A6–1. Study treatment with mosunetuzumab, tiragolumab, and atezolizumab should be permanently discontinued unless the criteria described in Table A6–1 are met.

Table A6–1 Recommendations for Management of Cytokine Release Syndrome and Infusion-Related Reactions for Participants Receiving Mosunetuzumab, Tiragolumab, and Atezolizumab (if applicable)

CRS Grade [a]	Action with Tiragolumab or Atezolizumab Infusion	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 1 fever ≥ 38°C [b]	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic *medications*, and/or analgesics, and monitor closely for IRRs and/or CRS.	• Symptomatic management of constitutional symptoms and organ toxicities • Consider empiric broad spectrum antibiotics. • Consider G-CSF if participant is neutropenic. • Maintenance IV fluids for hydration • Consider hospitalization until symptoms completely resolve.	• For prolonged CRS (> 2 days) in participants with significant symptoms and/or comorbidities (per investigator discretion [e.g., impaired cardiovascular function, reduced pulmonary reserve]), consider tocilizumab and corticosteroids as per Grade 2	• Administer premedications for next dose per Section 6.1.1. • Consider hospitalization of participant for next dose if it is a higher dose.

Table A6–1 Recommendations for Management of CytokineRelease Syndrome and Infusion-Related Reactions for Participants Receiving Mosunetuzumab, Tiragolumab, and Atezolizumab (if applicable) (cont.)

CRS Grade [a]	Action with Tiragolumab or Atezolizumab Infusion	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 2 fever ≥ 38°C [b] with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic *medications*, and/or analgesics, and monitor closely for IRRs and/or CRS.	• Symptomatic management of constitutional symptoms and organ toxicities • Consider ICU admission for hemodynamic monitoring. • For hypotension: IV fluid bolus as needed; for persistent refractory hypotension (e.g., after 2 fluid boluses and anti-IL-6 therapy), start vasopressors and manage per Grade 3. • Rule out other inflammatory conditions, which can mimic severe CRS (e.g., infections/sepsis). • Consider empiric broad spectrum antibiotics. • If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH as described in Section A6-2.3.	• Consider tocilizumab. [c] • For persistent refractory hypotension after 1 or 2 doses of anti–IL-6 therapy, consider 10 mg IV dexamethasone every 6 hours (or equivalent). • Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.	• May receive the next dose of mosunetuzumab if symptoms resolve to Grade 1 or better for 3 consecutive days. • Consider enhanced premedications for next dose. • Consider hospitalization of participant for next dose if it is a higher dose. [e]

Table A6–1 Recommendations for Management of Cytokine Release Syndrome and Infusion-Related Reactions for Participants Receiving Mosunetuzumab, Tiragolumab, and Atezolizumab (if applicable) (cont.)

CRS Grade [a]	Action with Tiragolumab or Atezolizumab Infusion	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 3 fever ≥ 38°C [b] with hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen by nasal cannula, face mask, nonrebreather mask, or Venturi mask	• Immediately stop infusion. • Permanently discontinue tiragolumab and atezolizumab (if applicable) and contact *the* Medical Monitor. [i]	• Symptomatic management of organ toxicities, admit participant to ICU for hemodynamic monitoring • For hypotension: IV fluid bolus and vasopressors as needed • Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections or sepsis). • Consider empiric broad spectrum antibiotics. • If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH (see Section A6–2.3).	• Administer tocilizumab [c] • Dexamethasone 10 mg IV every 6 hours (or equivalent). If refractory, manage as per Grade 4. [c] • Manage per Grade 4, if no improvement within 18–24 hours after second dose of tocilizumab.	• May receive the next dose of mosunetuzumab if CRS event was responsive to treatment (i.e., clinical improvement within 8–12 hours following tocilizumab/corticosteroids administration) and symptoms resolve to Grade ≤ 1 for 3 consecutive days. • 72-hour hospitalization with enhanced premedications for next dose. • If Grade 3 CRS occurs after the 5-mg injection, the next mosunetuzumab dose should again be 5 mg. If the next dose is tolerated without Grade 3 or higher CRS, the subsequent dose may be increased to 45 mg (per step up dose planned). • If Grade 3 CRS occurs after a 45-mg injection, the next mosunetuzumab dose should be reduced to 20 mg. If the next dose is tolerated without Grade 3 or higher CRS, the subsequent dose may be re-escalated to 45 mg. • If Grade 3 CRS recurs with subsequent doses, permanently discontinue mosunetuzumab. [i]

Table A6–1 Recommendations for Management of Cytokine Release Syndrome and Infusion-Related Reactions for Participants Receiving Mosunetuzumab, Tiragolumab, and Atezolizumab (if applicable) (cont.)

CRS Grade [a]	Action with Tiragolumab or Atezolizumab Infusion	Supportive Care	Anti–IL-6 or Corticosteroid Therapy	Action for Next Mosunetuzumab Dose
Grade 4 fever ≥ 38° [b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., C-PAP, BiPAP, intubation, and mechanical ventilation)	• Immediately stop infusion. • Permanently discontinue tiragolumab and atezolizumab (if applicable) and contact the Medical Monitor. [f]	• ICU admission and hemodynamic monitoring • Mechanical ventilation as needed • IV fluids and vasopressors as needed • Symptomatic management of organ toxicities • Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections or sepsis). • Consider empiric broad spectrum antibiotics. • If no improvement within 24 hours, initiate work up and assess for signs and symptoms of HLH (see Section A6–2.3).	• Administer tocilizumab. [c] • For participants refractory to tocilizumab, consider siltuximab, anakinra, dasatinib, and emapalumab, based on discretion of the investigator; management should be discussed with the Medical Monitor. [g] • Administer 10 mg IV dexamethasone every 6 hours (or equivalent). • If refractory, consider 1000 mg/day IV methylprednisolone. [h, i]	• Permanently discontinue mosunetuzumab [j]

Table A6–1 Recommendations for Management of Cytokine Release Syndrome and Infusion-Related Reactions for Participants Receiving Mosunetuzumab, Tiragolumab, and Atezolizumab (if applicable) (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bilevel positive airway pressure; C-PAP = continuous positive airway pressure; CRS = cytokine release syndrome; G-CSF = granulocyte colony–stimulating factor; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit.

[a] Cytokine release syndrome will be assessed according to the ASTCT Consensus Grading Scale Criteria (Lee et al. 2019; see Appendix 9). Fever is defined as temperature ≥38°C not attributable to any other cause. In participants who have CRS and then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. Cytokine release syndrome grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

[b] As participants may have received corticosteroid premedication, a fever response may be blunted. Therefore, adverse events attributed to mosunetuzumab consistent with a diagnosis of IRR or CRS, and associated with fever, hypotension or hypoxia not attributable to any other cause, should be recorded as CRS. Cytokine release syndrome events that manifest with hypotension and/or hypoxia but with no fever should be graded depending on management required for hypotension and/or hypoxia. These types of events correspond to minimum ASTCT Grade 2. Other adverse events occurring within 24 hours after mosunetuzumab administration should be reported as individual adverse events (e.g., headache or chills).

[c] See Appendix 8 for tocilizumab treatment for CRS. Tocilizumab should be administered by IV infusion at a dose of 8 mg/kg (8 mg/kg for participants weighing ≥30 kg only and 12 mg/kg for participants weighing <30 kg; doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (for up to a maximum of 4 doses).

[d] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

[e] Hospitalization is required for subsequent mosunetuzumab doses following a Grade ≥2 CRS event for participants in the Safety Run-In phase.

[f] Resumption of tiragolumab and atezolizumab (if applicable) may be considered in participants who are deriving benefit and have fully recovered from the event. The decision to re-challenge participants with tiragolumab and atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator after consultation with the Medical Monitor as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretic *medications*, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit–risk ratio.

[g] Riegler et al. 2019.

[h] Antifungal prophylaxis should be strongly considered in participants receiving steroids for treatment of CRS.

[i] For example, 1000 mg/day IV methylprednisolone for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 13 hours for 2 days, and 60 mg every 12 hours for 2 days.

Table A6–1 Recommendations for Management of Cytokine Release Syndrome and Infusion-Related Reactions for Participants Receiving Mosunetuzumab, Tiragolumab, and Atezolizumab (if applicable) (cont.)

[i] Resumption of mosunetuzumab may be considered in participants who are deriving benefit and have fully recovered from the adverse event. Participants can be re-challenged with mosunetuzumab only after approval has been documented by the investigator and after consultation with the Medical Monitor. Further treatment should not be considered unless all the criteria below are met:

- Individual benefit–risk assessment by Principal Investigator/treating physician favors continued treatment.
- The participant has recovered from previous toxicities and has sufficient organ function/reserve to receive subsequent doses.
- The participant has been adequately consented for risks associated with continued treatment and decides to receive subsequent doses.
- The above benefit–risk assessment and evaluation of participants are discussed with the Sponsor.
- Subsequent doses are well planned with precautionary measures, including dose reduction, mandatory hospitalizations, and enhanced premedications.

A6–2.3.2 Neutropenia and Febrile Neutropenia

All participants should be monitored at each cycle for neutropenia, and participants experiencing neutropenia should undergo blood cell monitoring until resolution of the event to Grade 2. Guidelines for neutropenia management are outlined in Table A6–2. Participants who experience febrile neutropenia should be managed according to local guidelines or as per institutional practice.

Table A6–2 Management Guidelines for Neutropenia (including Febrile Neutropenia)

Grade	Management
Grade 1 or 2	• Manage according to institutional practice. • The mosunetuzumab step-up doses on C1D8 and C1D15 should not be held for uncomplicated neutropenia.
Grade 3 or 4	• Delay all study treatment until ANC recovery following guidelines below, with the exception that the mosunetuzumab step-up doses on C1D8 and C1D15 should not be held for uncomplicated neutropenia. • Growth factors (e.g., G-CSF) for neutropenia are permitted. • Consider holding study treatment for persistent Grade 4 neutropenia (>21 days after the scheduled dose of the next cycle). • Discontinue study treatment if neutropenia of Grade 4 severity is observed 3 times across 3 separate treatment cycles. • The dose of mosunetuzumab, tiragolumab, or atezolizumab should not be modified.

C=cyle; D=day; G-CSF=granulocyte colony–stimulating factor.

A6–2.3.3 Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

In the setting of T-cell engaging therapies including mosunetuzumab, CRS is much more likely compared with secondary HLH and MAS. Considering the overlapping presentation of symptoms, management of these participants should be primarily focused on treatment of CRS (see Table A6–1).

In atypical cases such as late onset CRS (past completion of step-up dosing with mosunetuzumab) or CRS that is refractory to treatment, work-up for HLH should be initiated, and all cases of suspected HLH should be discussed with the Medical Monitor immediately. While there is no currently universally accepted set of criteria for diagnosing secondary or reactive HLH in the adult population, proposed criteria have been published (Henter et al. 2007, Fardet et al. 2014; Hejblum et al. 2014; McClain and Eckstein 2014).

The supportive management of HLH is generally similar to that of CRS. Specific diagnostic, monitoring and management guidelines for HLH are described below.

Participants with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A participant should be classified as having HLH if five of the following eight criteria are met:

- Fever $\geq$38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $<$90 g/L (9 g/dL; $<$100 g/L [10 g/dL] for infants $<$4 weeks old)
  - Platelet count $<100x10^9$/L (100,000/μL)
  - ANC $<1.0x10^9$/L (1000/μL)
- Fasting triglycerides $>$2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent NK cell activity
- Ferritin $>$500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated $\geq$2 standard deviations above age-adjusted laboratory-specific norms

In all cases of suspected HLH, the Medical Monitor should be immediately notified. Participants should be hospitalized with the following diagnostic and monitoring measures initiated:

- Frequent (e.g., every 4 hours) vital signs and physical examination, including evaluation for splenomegaly
- Serial (at least daily) monitoring of serum chemistries, complete blood counts, LFTs, PT/PTT, fibrinogen, D-dimer, and triglycerides
- Consideration of bone marrow and/or lymph node biopsy to assess for hemophagocytosis and active infection, including assessment of EBV protein localization in T/B/NK cells
- Complete infectious disease work-up, including the following:
  - Blood cultures (bacterial and fungal)
  - Urine cultures and urinalysis
  - Radiographic assessments (e.g., chest X-ray or CT scan)
  - Assessment for active viral infections, including but not limited to EBV and cytomegalovirus (CMV)
- If available, assessment for soluble CD25 and assessment of NK cell function

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin >684 mg/L (>684 ng/mL)
- At least two of the following:
  - Platelet count ≤181 × 10^9/L (≤181,000/μL)
  - AST ≥48 U/L
  - Triglycerides >1.761 mmol/L (>156 mg/dL)
  - Fibrinogen ≤3.6 g/L (≤360 mg/dL)

Participants with suspected HLH or MAS should be treated according to the guidelines in Table A6–3. In the case of confirmed HLH, permanently discontinue study treatment with mosunetuzumab, tiragolumab, and atezolizumab.

Table A6–3 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected or Confirmed HLH or MAS	• Permanently discontinue mosunetuzumab, atezolizumab, and tiragolumab and contact the Medical Monitor. • Refer participant to a hematologist. • Institute appropriate supportive care, including intensive care monitoring, if indicated per the institutional guidelines. • Treat with appropriate HLH therapy according to institutional standards or published references (Schram and Berliner 2015; Vallurupalli and Berliner 2019). • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact *the* Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

A6–2.3.4 Injection Site Reactions

Participants who experience localized injection site reactions following SC administration of mosunetuzumab should be managed according to the guidelines detailed in Table A6-4.

Table A6-4 Management Guidelines for Injection Site Reactions

Grade	Management
Grade 1	• Consider treatment with topical steroids. • Continue mosunetuzumab in subsequent cycles.
Grade 2	• Notify Medical Monitor. • Initiate treatment with topical steroids. • If progressive after 24 hours, consider prednisone or equivalent 10–30 mg/day. • Continue mosunetuzumab in subsequent cycles after improvement to Grade ≤ 1.
Grade 3	• Notify Medical Monitor. • Withhold mosunetuzumab. • Initiate prednisone 1 mg/kg/day or equivalent. • Obtain a dermatology consultation. • Taper steroids after improvement to Grade ≤ 1. • Continue mosunetuzumab in subsequent cycles after improvement to Grade ≤ 1.
Grade 4	• Notify Medical Monitor. • Management as for Grade 3. • Permanently discontinue SC mosunetuzumab.

A6–2.3.5 Neurologic Adverse Events

Neurologic adverse events will be monitored closely during the trial. All participants will be required to undergo a baseline neurologic examination as part of the physical exam (See Section 1.3 and Section 8.2.1) prior to the first mosunetuzumab administration.

Participants should be routinely assessed for any signs or symptoms of neurologic adverse events as part of the on-treatment clinical examination. If new or worsening neurologic adverse events are suspected, the participant should be referred to a neurologist for further evaluation of potential drug-related neurotoxicity. Corticosteroids should be considered to treat suspected neurologic toxicity. Imaging studies (e.g., diffusion-weighted MRI) should be performed if clinically indicated (see Table A6–5).

Decisions on whether to continue or to hold study treatment for any Grade 1 neurologic adverse events will be at the discretion of the study investigator. For Grade ≥2 neurologic adverse events, study treatment should be held until the event returns to baseline for at least 3 days without any medication. If restarting study treatment following adverse event resolution, *decisions regarding dose and schedule modifications will be made following individual benefit–risk assessment by the investigator and* in *consultation with the Medical Monitor.* For Grade 3 neurologic adverse events lasting >7 days, the overall benefit–risk of continued study treatment should be assessed by the study investigator in consultation with the Medical Monitor. If the Grade 3 neurologic adverse event recurs in any subsequent cycles, study treatment should be permanently discontinued.

Study treatment should be permanently discontinued for Grade ≥3 seizures.

Participants who develop a neurologic adverse event that may affect driving and for participants who develop CRS, HLH, or Grade 3 or 4 LFT elevation, the investigator should advise them to refrain from driving or engaging in hazardous occupations or activities until the event is resolved. Neurologic adverse events with the potential to impact cognition or consciousness that may affect driving (driving-impacting cognition or consciousness neurologic events) include but are not limited to amnesia, aphasia, confusional state, delirium, depressed level of consciousness, disturbance in attention, encephalopathy, hallucination, hepatic encephalopathy, insomnia, memory impairment, seizure, visual hallucination, and vertigo.

Participants who develop other neurologic adverse events such as tremor or dizziness should be assessed by neurologic examination to determine if the adverse event may impair the ability of the participant to drive or engage in hazardous occupations or activities. For participants assessed to be at increased risk, the investigator should advise them to refrain from driving or engaging in hazardous occupations or activities until the event is resolved.

Management guidelines for neurologic adverse events are summarized in Table A6–5, *with specific guidelines for immune-mediated myelitis associated with tiragolumab* and/*or* atezolizumab *treatment provided in* Table A6–6.

Table A6-5 Management Guidelines for Neurologic Adverse Events

Event	Grade	Management
Seizure	Grade 1 or 2	• Withhold further study treatment, provide supportive care. • Consider treatment with corticosteroids. • Obtain neurology consultation; consider brain MRI (with diffusion-weighted imaging), lumbar puncture, EEG. • Study treatment may be resumed if no recurrent seizure for at least 3 days and with confirmation of baseline neurologic examination. [a, c]
	Grade 3 or 4	• Permanently discontinue study treatment. • Consider treatment with corticosteroids. • Obtain neurology consultation.
Immune-mediated neuropathy	Grade 1	• Continue study treatment. • Investigate etiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
	Grade 2, *including facial paresis*	• Withhold study treatment. • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. *For general immune-mediated neuropathy:* • If event resolves to Grade 1 *or better, resume tiragolumab and atezolizumab.* [a, b, c] • *If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab,* permanently discontinue *tiragolumab and atezolizumab and contact the* Medical Monitor. [a, b, d] *For facial paresis:* • *If event resolves fully, resume tiragolumab and atezolizumab.* [b] • *If event does not resolve fully while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact the Medical Monitor.* [c]

Table A6–5 Management Guidelines for Neurologic Adverse Events (cont.)

Event	Grade	Management
Immune-mediated neuropathy (cont.)	Grade 3 or 4, *including facial paresis (cont.)*	• Permanently discontinue study treatment and notify Medical Monitor. [d] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Neurologic events, not otherwise specified	Grade 1	• Notify Medical Monitor. • Consider withholding study treatment during evaluation.
	Grade 2	• Notify Medical Monitor. • Withhold further study treatment. • Consider treatment with corticosteroids. • Consider neurology consultation. • Study treatment may be resumed when symptoms have returned to baseline ≥ 3 consecutive days without the need for medical management and with confirmation of baseline neurologic examination. [a]
	Grade 3	• Notify Medical Monitor. • Withhold further study treatment. • Consider treatment with corticosteroids. • Obtain neurology consultation. • Consider discontinuation of study treatment if symptoms persist > 7 days. [e] • Study treatment may be resumed when symptoms have returned to baseline ≥ 3 consecutive days without the need for medical management and with baseline neurologic examination. [a] – Dose reduce mosunetuzumab per Section A6–2.1 if resuming. • Permanently discontinue study treatment for recurrent Grade 3 event.
	Grade 4	• Notify Medical Monitor. • Permanently discontinue study treatment. • Obtain neurology consultation.

Table A6–5 Management Guidelines for Neurologic Adverse Events (cont.)

MRI = magnetic resonance imaging.

[a] Study treatment may be withheld for a period of time beyond 12 weeks to allow corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before tiragolumab and atezolizumab (if applicable) can be resumed.

[c] The Medical Monitor is available to advise as needed.

[d] Resumption of study treatment may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with study treament should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

[e] The overall benefit–risk of continued treatment with study treatment should be assessed by the study investigator in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-6 Management Guidelines for Immune-Mediated Myelitis

Event	*Management*
Immune-mediated myelitis, Grade 1	• *Continue tiragolumab and atezolizumab unless symptoms worsen or do not improve.* • *Investigate etiology and refer patient to a neurologist.*
Immune-mediated myelitis, Grade 2	• *Permanently discontinue tiragolumab and atezolizumab and contact the Medical Monitor.* • *Investigate etiology and refer patient to a neurologist.* • *Rule out infection.* • *Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.*
Immune-mediated myelitis, Grade 3 or 4	• *Permanently discontinue tiragolumab and atezolizumab and contact the Medical Monitor.* • *Refer patient to a neurologist.* • *Initiate treatment as per institutional guidelines.*

A6–2.3.6 Tumor Lysis Syndrome

As mosunetuzumab and tiragolumab have the potential for potent B-cell killing, all participants will receive prophylaxis for TLS based on the prophylaxis guidelines below.

Upon hospital admission for Cycle 1 study treatment administration, the participant's serum chemistry and hematology laboratory samples should be obtained and reviewed, and prophylactic measures initiated according to the guidelines described below. Access to nephrologist and acute dialysis services must be available in the event of clinically significant TLS (see Table A6–7). Telemetry should also be considered.

All participants will receive prophylaxis for TLS prior to each mosunetuzumab administration at C1D1, C1D8, and C1D15. Prophylaxis guidelines include the following:

- *All participants should receive adequate* hydration, consisting of a fluid intake of approximately 2–3 L/day starting 24–48 hours prior to the first dose of mosunetuzumab.
  - If a participant is hospitalized for the administration of study treatment, IV hydration at a rate of 150–200 mL/hour should begin at the conclusion of mosunetuzumab administration and continue for at least 24 hours thereafter.
  - If a participant receives study treatment in the outpatient setting, fluid intake should be maintained at 2–3 L/day for at least 24 hours after mosunetuzumab administration.
  - Modification of fluid rate should be considered for individuals with specific medical needs.
- *In addition,* administration of an agent to reduce uric acid *should be considered*:
  - Allopurinol (e.g., 300 mg/day orally beginning 72 hours prior to dose and continuing for 3–7 days afterwards) for those participants judged to be of low or intermediate risk of developing TLS per the investigator's discretion.
  - For participants with elevated uric acid levels prior to mosunetuzumab treatment, or considered to be at high risk for TLS: rasburicase (e.g., 0.2 mg/kg IV over 30 minutes prior to first dose mosunetuzumab and daily for up to 5 days thereafter) should be administered, unless contraindicated (Elitek® USPI).
  - Treatment with allopurinol or rasburicase should continue as specified above, or if laboratory evidence of TLS is observed until normalization of serum uric acid or other lab parameters.
  - If treatment with allopurinol or rasburicase is contraindicated or is otherwise inappropriate in the view of the investigator, the Medical Monitor is available to advise as needed. Laboratory monitoring for tumor lysis is described in the schedule of activities (Section 1.3).
- Note that uric acid measurement in the presence of rasburicase administration requires special handling (Elitek USPI).

Due to the risk of TLS following mosunetuzumab and tiragolumab administration, participants must have a normal creatinine or a creatinine clearance ≥50 mL/min to

participate in this trial (Section 5.1). Laboratory results should be reviewed, and electrolyte values should not demonstrate any clinically significant abnormalities prior to the administration of mosunetuzumab in Cycle 1 and beyond; otherwise the participant should receive additional prophylactic treatment and hydration prior to the initiation of dosing. Laboratory abnormalities suggestive of TLS should prompt immediate action by the treating clinicians, and TLS should be treated aggressively per institutional practice.

Participants at high risk for TLS should continue to receive prophylaxis with allopurinol or rasburicase and adequate hydration with each subsequent dose of mosunetuzumab until the participant is no longer considered to be at risk for TLS. Participants who develop either clinical or laboratory TLS during Cycle 1 should be considered for hospitalization (i.e., through at least 72 hours after study treatment administration) during subsequent cycles for optimum hydration and monitoring.

Laboratory values obtained for TLS monitoring need not be entered in the electronic Case Report Forms except as indicated in Section 1.3 and Table A6–7 unless a diagnosis of TLS (laboratory or clinical) is made.

If the Howard criteria for TLS (see Table A6–7) are fulfilled at any time during the study (two or more electrolyte laboratory abnormalities present simultaneously) or if there is a medically relevant laboratory abnormality in TLS-related parameters or a sign of clinical TLS (e.g., increased serum creatinine or cardiac dysrhythmia), study treatment should be withheld and participants should be hospitalized and adequately treated until normalization of laboratory abnormalities before treatment is restarted (Howard et al. 2011). Treatment for laboratory and/or clinical presentations of TLS will follow institutional practice.

Table A6-7 Definitions of Laboratory and Clinical Tumor Lysis Syndrome

Metabolic Abnormality	Criteria for Classification of Laboratory TLS[a]	Criteria for Classification of Clinical TLS[a]
Hyperuricemia	Uric acid ≥ 8.0 mg/dL (475.8 μmol/L)	–
Hyperphosphatemia	Phosphorous >4.5 mg/dL (1.5 mmol/L)	–
Hyperkalemia	Potassium >6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL (1.75 mmol/L) or ionized calcium <4.5 mg/dL (<1.12 mml/L)[b]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury[c]	Not applicable	Increase of 0.3 mg/dL (26.5 μmol/L) in serum creatinine level (or a single value >1.5 × age-appropriate ULN range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hr for 6 hours

TLS=tumor lysis syndrome; ULN=upper limit of normal.

Source: Howard et al. 2011.

Note: TLS should be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

[a] In laboratory TLS, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical TLS requires the presence of laboratory TLS plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

[b] The corrected calcium level in milligrams per deciliter-measured calcium level in milligrams per deciliter +0.8 × (4–albumin in grams per deciliter).

[c] Acute kidney injury is defined as an increase of 0.3 mg/dL (26.5 μmol/L) in creatinine level or a period of oliguria lasting 6 or more hours. By definition, if acute kidney injury is present, the participant has clinical TLS (Levin et al. 2007).

A6–2.3.7 Infections

Treatment for infections will follow institutional practice. Mosunetuzumab, tiragolumab, and atezolizumab should not be administered in the presence of active severe infections *or active SARS-COV-2 infections.*

In the setting of a pandemic or epidemic, screening for active infections prior to and during study participation should be considered according to local/institutional guidelines or those of applicable professional societies (e.g., American Society of Clinical Oncology, European Society for Medical Oncology).

To ensure study treatment administration does not occur in the presence of active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, local PCR or antigen testing is recommended during screening; PCR testing is preferred.

If the participant develops SARS-CoV-2 infection during study treatment, study treatment should be interrupted. The infection must be clinically resolved before resumption of study treatment.

A positive PCR test for SARS-COV-2 infection in an asymptomatic individual may be a sign of possible active infection that would require interruption of study therapy and clinical evaluation to assess the clinical course of the infection and administration of appropriate COVID-19 directed therapies.

Investigators must rule out active infection (e.g., by clinical evaluation of respiratory symptoms, radiological tests to confirm absence of pneumonia, consideration of negative serial viral testing) and assess benefit–risk prior to resuming study treatment.

Signs and symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment.

Particular attention should be given to participants who have had significant prior immunosuppressive treatment such as high dose chemotherapy. Progressive multifocal leukoencephalopathy (PML) has been associated with treatment with CD20-directed therapies including rituximab and obinutuzumab. The diagnosis of PML should be considered in any participant presenting with new-onset neurologic manifestations and consultation with a neurologist and diagnostic procedures including brain MRI and lumbar puncture should be performed as clinically indicated. Note, however, that new-onset neurologic adverse events following initial doses of mosunetuzumab may be more likely due to acute effects of mosunetuzumab as PML associated with rituximab generally occurred following long-term exposure (Carson et al. 2009).

For management of participants who demonstrate evidence of hepatitis reactivation, *see Section A6–1.1.4.*

A6–2.3.8 Thrombocytopenia

All participants should be monitored at each cycle for thrombocytopenia, and participants experiencing thrombocytopenia should undergo blood cell monitoring until resolution of

the event to Grade 1 (platelet count ≥75,000/μL). Guidelines for thrombocytopenia management are outlined in Table A6–8.

Table A6-8 Management Guidelines for Thrombocytopenia

Event	Management
Cycle 1: Grade 2, 3, or 4 (platelet count <75,000/μL)	• Mosunetuzumab step-up doses should not be held for uncomplicated thrombocytopenia. • The dose of mosunetuzumab, tiragolumab, and atezolizumab (if applicable) should not be modified.
Cycles 2–17: Grade 3 or 4 (platelet count <50,000/μL)	Delay all study treatment until platelet recovery following guidelines below: • If platelet count recovers to ≥50,000/μL within ≤14 days after the scheduled date for the next cycle, administer the full dose of all study treatments. • If platelet count recovers to ≥50,000/μL within 14–21 days after the scheduled date for the next cycle, the participant may continue study treatment with mosunetuzumab at the investigator's discretion. • Consider holding mosunetuzumab for persistent Grade 3 or higher thrombocytopenia (>21 days after the scheduled dose of the next cycle). • Discontinue study treatment if thrombocytopenia of Grade 4 severity is observed 3 times across 3 separate treatment cycles. • The dose of mosunetuzumab, tiragolumab, and atezolizumab (if applicable) should not be modified.

A6–2.3.9 Elevated Liver Enzymes and Hepatic Events

Participants with right upper quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

Liver function tests will be assessed regularly during study and should be managed according to guidelines in Table A6-9.

For participants with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Note that transient Grade 3 AST elevation in the setting of Grade 2 CRS as well as Grade 3 hepatic encephalopathy or Grade 4 elevation in LFTs have been observed following mosunetuzumab treatment, and immune-mediated hepatitis has been associated with the administration of atezolizumab; management guidelines describe actions with respect to both mosunetuzumab and atezolizumab.

Table A6-9 Management Guidelines for Liver Function Test Abnormalities and Hepatic Events

LFT Abnormality	Management
Grade 1 AST or ALT elevation	• Continue study treatment. • Contact Medical Monitor and monitor LFTs (including AST, ALT, and bilirubin) weekly.
Grade 2 AST or ALT elevation	**All events:** • Withhold further study treatment. • Monitor LFTs at least weekly and as clinically indicated until values resolve to normal or baseline. • Consider hepatology consultation. **Events > 5 days' duration:** • If event is immune related, [a] initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. – If event resolves to Grade ≤ 1, taper corticosteroids per institutional practice. [b] • Resume study treatment when resolved to Grade ≤ 1 or baseline within 12 weeks. [c, d] • If event does not resolve to Grade ≤ 1 or baseline within 12 weeks permanently discontinue study treatment. [e]
Grade 3 AST or ALT elevation	**All events:** • Withhold further study treatment. • Monitor LFTs every 24–48 hours until decreasing, then follow weekly. • Obtain hepatology consultation, consider liver biopsy to assess hepatic injury. • If event is immune related, [a] initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. – If no improvement within 48 hours after initiating corticosteroids, consider additional immunosuppressive agent(s). – If event resolves to Grade ≤ 1, taper corticosteroids per institutional practice (single-agent mosunetuzumab) or over ≥ 1 month for (participants receiving tiragolumab and/or atezolizumab). [b, d] **Events >5 days' duration:** • Permanently discontinue study treatment. [e]
Grade 4 AST or ALT elevation	• Permanently discontinue study treatment. [e] • Follow management guidelines as described for Grade 3 events.

LFT=liver function test; ULN=upper limit of normal.

Table A6–9 Management Guidelines for Liver Function Test Abnormalities and Hepatic Events (cont.)

[a] Immune-mediated event should be considered when concurrent clinical and laboratory manifestations of CRS and/or HLH are present, or in instances where no alternative etiology (e.g., viral, neoplastic) can account for observed LFT abnormalities.

[b] For participants receiving tiragolumab and atezolizumab (if applicable), if corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before tiragolumab and atezolizumab can be resumed.

[c] Tiragolumab and atezolizumab (if applicable) may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] Consideration for earlier resumption of study treatment for participants receiving combination treatment may be consulted with the Medical Monitor.

[e] Resumption of study treatment may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants may resume dosing with study treatment only after documented approval by the investigator. The Medical Monitor is available to advise as needed. Mosunetuzumab dose and schedule modifications as described in Section A6–2.1 apply when considering resuming study treatment.

A6–2.3.10 Tumor Flare

The recognition of tumor flare may be supported by clinical presentation and temporal association. Tumor flare events tend to have an early onset (Cycles 1 and 2), are transient, and affect organ systems in proximity to tumor involvement. When medically feasible and clinically indicated, a biopsy of the involved site should be obtained to confirm the diagnosis of tumor flare (characterized by immune cell infiltrates) and to rule out other causes, including infection and disease progression. If the clinical presentation involves a new or worsening pleural or pericardial effusion or ascites, a sample of the fluid may be collected and analyzed.

Patients with tumors involving critical anatomic locations should be closely monitored for tumor flare, and prospective preventive or interventional measures may need to be considered or planned prior to dosing.

A6–2.3.11 Pulmonary Events

Participants will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary

hypertension. Management guidelines for pulmonary events associated with atezolizumab are described in Table A6-10.

Table A6-10 Management Guidelines for Pulmonary Events, Including Pneumonitis

Grade	Management
Grade 1	• Continue study treatment and monitor closely. • Re-evaluate on serial imaging. • Consider participant referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab and tiragolumab.
Grade 2	• Withhold study treatment for up to 12 weeks after event onset. [a] • Refer participant to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • Resume study treatment if event resolves to Grade 1 or better within 12 weeks. [a, b, c] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment and contact *the* Medical Monitor. [a, b, d, e] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Grade 3 or 4	• Permanently discontinue study treatment and contact Medical Monitor. [d, e] • *Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.* • Bronchoscopy or BAL *with or without transbronchial biopsy* is recommended. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Table A6–10 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

BAL = bronchoscopic alveolar lavage; IVIG = intravenous immunoglobulin.

[a] Study treatment may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Consideration for earlier resumption of mosunetuzumab and tiragolumab for participants receiving combination treatment may be consulted with the Medical Monitor.

[d] Resumption of study treatment may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with study treament should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

[e] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

A6–2.3.12 Gastrointestinal Events

Management guidelines for diarrhea or colitis are provided in Table A6-11.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased CRP, platelet count, or bandemia): perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table A6-11 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Grade	Management
Grade 1	• Continue study treatment. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Grade 2	• Withhold study treatment. [a] • Initiate symptomatic treatment. • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Participant referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. *If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume study treatment. [a, b, c] • Permanently discontinue study treatment and contact *the* Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, d]
Grade 3	• Withhold study treatment. • Refer participant to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • Resume study treatment if event resolves to Grade 1 or better within 12 weeks. [a, b, c] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment and contact *the* Medical Monitor. [a, b, d]
Grade 4	• Permanently discontinue study treatment and contact *the* Medical Monitor. [d] • Refer participant to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Table A6–11 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

[a] Study treatment may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study treatment can be resumed.

[c] Consideration for earlier resumption of study treatment for participants receiving combination treatment may be consulted with the Medical Monitor.

[d] Resumption of study treatment may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with study treament should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

A6–2.3.13 Endocrine Events

Participants with unexplained symptoms such as headache, fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The participant should be referred to an endocrinologist if an endocrinopathy is suspected. TSH and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

See Table A6-12 for management guidelines.

Table A6-12 Management Guidelines for Endocrine Events

Event and Grade	Management
Grade 1 hypothyroidism	• *Continue study treatment.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH closely.*
Grade 2 hypothyroidism	• *Consider withholding* study treatment. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • *Consider patient referral to endocrinologist.* • *Resume study treatment when symptoms are controlled and thyroid function is improving.*
Grade 3 and 4 hypothyroidism	• Withhold study treatment. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • *Refer* to *an* endocrinologist. • *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).* • Resume study treatment when symptoms are controlled, and thyroid function is improving. [a] • *Permanently discontinue study treatment and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.* [b]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue study treatment. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• *Consider withholding study treatment.* • *Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.* • *Consider patient referral to endocrinologist.* *Resume study treatment when symptoms are controlled and thyroid function is improving.*

Table A6-12 Management Guidelines for Endocrine Events (cont.)

Event and Grade	Management
Grade 3 and 4 hyperthyroidism	• Withhold study treatment. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to an endocrinologist. • Resume study treatment when symptoms are controlled, and thyroid function is improving. [a] • Permanently discontinue study treatment and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [b]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold study treatment. [c] • Refer participant to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume study treatment if event resolves to Grade 1 or better and participant is stable on replacement therapy (if required) within 12 weeks. [a, c, d] • Permanently discontinue study treatment and contact the Medical Monitor if event does not resolve to Grade 1 or better or participant is not stable on replacement therapy within 12 weeks. [b, c, d]
Hyperglycemia, Grade 1 or 2	• Continue study treatment. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold study treatment. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume study treatment when symptoms resolve, and glucose levels are stable. [a]

Table A6-12 Management Guidelines for Endocrine Events (cont.)

Event and Grade	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold study treatment. [c] • Refer participant to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. [c] • Initiate hormone replacement as clinically needed. • Resume study treatment if event resolves to Grade 1 or better within 12 weeks. [c, d] • *If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment and contact the Medical Monitor.* [b] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue study treatment and contact *the* Medical Monitor. [b] • Refer participant to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 12 mg/kg/day oral prednisone or equivalent upon improvement. [c] • Initiate hormone replacement as clinically needed.

MRI = magnetic resonance imaging.

[a] Consideration for earlier resumption of study treatment may be consulted with the Medical Monitor.

[b] Resumption of study treatment may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with study treatment should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

[c] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study treatment can be resumed.

[d] Study treatment may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed

A6–2.3.14 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A6-13.

Table A6-13 Management Guidelines for Ocular Events

Grade	Management
Grade 1	• Continue study treatment. • Participant referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Grade 2	• Withhold study treatment for up to 12 weeks after event onset. [a] • Participant referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • Resume study treatment if event resolves to Grade 1 or better within 12 weeks. [a, b, c] • Permanently discontinue study treatment and contact *the* Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, d]
Grade 3 or 4	• Permanently discontinue study treatment and contact Medical Monitor. [d] • Refer participant to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Study treatment may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study treatment can be resumed.

[c] Consideration for earlier resumption of study treatment may be consulted with the Medical Monitor.

[d] Resumption of study treatment may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with study treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A6–2.3.15 Pancreatic Events

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table A6-14.

Table A6-14 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event and Grade	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase >1.5–2.0 × ULN:** • Continue study treatment. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase >2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold study treatment for up to 12 weeks after event onset. [a, b] • Refer participant to gastrointestinal specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume study treatment. [a, b, c] • Permanently discontinue study treatment and contact *the* Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, d] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [d]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold study treatment. • Refer participant to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume study treatment if event resolves to Grade 1 or better within 12 weeks. [a, b, c] • Permanently discontinue study treatment and contact *the* Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, d] • For recurrent events, permanently discontinue study treatment and contact *the* Medical Monitor. [d]

Table A6–14 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event and Grade	Management
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue study treatment and contact Medical Monitor.[d] • Refer participant to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Study treatment may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids, if initiated, to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] Consideration for earlier resumption of study treatment may be consulted with the Medical Monitor.

[c] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before study treatment can be resumed.

[d] Resumption of study treatment may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with study treatment should be based on *the* investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

A6–2.3.16 Dermatologic Events

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table A6-15.

Table A6-15 Management Guidelines for Dermatologic Events

Grade	Management
Grade 1	• Continue study treatment. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Grade 2	• Continue study treatment. • Consider participant referral to dermatologist *for evaluation and, if indicated, biopsy*. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Grade 3	• Withhold study treatment for up to 12 weeks after event onset. [a] • Refer participant to dermatologist *for evaluation and, if indicated, biopsy*. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume study treatment. [a, b, c] • Permanently discontinue study treatment and contact *the* Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, d]
Grade 4	• Permanently discontinue study treatment and contact Medical Monitor. [d]

Table A6-15 Management Guidelines for Dermatologic Events (cont.)

Grade	Management
Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade)	*Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:* • *Withhold study treatment for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.* • *Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy.* • *Follow the applicable treatment and management guidelines above.* • *If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue study treatment.*

[a] Study treatment may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids, if initiated, to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study treatment can be resumed.

[c] Consideration for earlier resumption of study treatment for participants receiving combination treatment may be consulted with the Medical Monitor.

[d] Resumption of study treatment may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with study treatment should be based on *the* investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.

A6–2.3.17 Immune-Mediated Meningoencephalitis, Gullian-Barré Syndrome, and Myasthenia Gravis

Immune-mediated meningoencephalitis should be suspected in any participant presenting with signs or symptoms suggestive of meningitis or encephalitis, including but not limited to headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All participants being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Participants with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the management guidelines in Table A6-16.

Table A6-16 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue study treatment and contact *the* Medical Monitor. • Refer participant to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. [a]
Myasthenia gravis and Guillain-Barré syndrome, all grades	• Permanently discontinue study treatment and notify *the* Medical Monitor. • Refer participant to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study treatment can be resumed.

A6–2.3.18 Immune-Mediated Myocarditis

Immune-mediated myocarditis should be suspected in any participant presenting with signs or symptoms suggestive of myocarditis, including but not limited to laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis *or associated with pericarditis (see section on pericardial disorders below)* and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral [e.g., participant may recall a recent history of gastrointestinal illness]), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All participants suspected for possible myocarditis should be urgently evaluated with cardiac enzymes, ECG, chest X-ray, echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial

biopsy may be considered for definitive diagnosis and appropriate treatment, if clinically indicated.

Participants with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-17.

Table A6-17 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grade 2–4 *Immune-mediated pericardial disorders, Grades 2–4*	• Permanently discontinue study treatment and contact *the* Medical Monitor. • Refer participant to cardiologist. • Initiate treatment as per institutional guidelines and consider temporary pacemaker, ECMO, VAD, or *pericardiocentesis* as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

A6–2.3.19 Renal Events

Participants with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as nonsteroidal anti-inflammatory drugs). Refer the participant to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Participants with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-18.

Table A6-18 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue mosunetuzumab, tiragolumab, and atezolizumab (if applicable). • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Continue mosunetuzumab unchanged or consider reduction of dose to 20 mg, if next dose is planned for 45 mg. • Withhold tiragolumab and atezolizumab (if applicable) for up to 12 weeks after event onset. [a] • Refer participant to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume tiragolumab and atezolizumab (if applicable). [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab (if applicable), permanently discontinue tiragolumab and atezolizumab (if applicable) and contact *the* Medical Monitor. [c]
Renal event, Grade 3 or 4	• Withold mosunetuzumab for Grade 3 event for up to 12 weeks until the event has resolved to Grade 1 or better and contact *the* Medical Monitor. [a] • If event does not resolve to Grade 1 or better while withholding mosunetuzumab, permanently discontinue mosunetuzumab and contact *the* Medical Monitor. [b, c] • Permanently discontinue mosunetuzumab for Grade 4 event and contact *the* Medical Monitor. • Permanently discontinue tiragolumab and atezolizumab (if applicable) and contact *the* Medical Monitor. • Refer participant to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Table A6–18 Management Guidelines for Renal Events (cont.)

[a] Mosunetuzumab, tiragolumab, and atezolizumab (if applicable) may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before mosunetuzumab, tiragolumab and atezolizumab (if applicable) can be resumed.

[c] Resumption of mosunetuzumab, tiragolumab and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with study treatment should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

A6–2.3.20 Immune-Mediated Myositis

Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Participants with possible myositis should be referred to a rheumatologist or neurologist. Participants with possible myositis should be monitored for signs of myocarditis.

Participants with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-19.

Table A6-19 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue mosunetuzumab, tiragolumab and atezolizumab (if applicable). • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Continue mosunetuzumab unchanged or consider reduction of dose to 20 mg, if next dose is planned for 45 mg. • Withhold tiragolumab and atezolizumab (if applicable) for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume tiragolumab and atezolizumab (if applicable). [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab (if applicable), permanently discontinue tiragolumab and atezolizumab (if applicable) and contact *the* Medical Monitor. [c]
Immune-mediated myositis, Grade 3	• Withhold mosunetuzumab, tiragolumab, and atezolizumab (if applicable) for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume mosunetuzumab, tiragolumab, and atezolizumab (if applicable). [b]

Table A6–19 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3 (cont.)	• If event does not resolve to Grade 1 or better while withholding mosunetuzumab, tiragolumab, and atezolizumab (if applicable), permanently discontinue mosunetuzumab, tiragolumab, and atezolizumab (if applicable) and contact the Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and tiragolumab and contact the Medical Monitor. [c]
Immune-mediated myositis, Grade 4	• Permanently discontinue mosunetuzumab, tiragolumab, and atezolizumab (if applicable) and contact the Medical Monitor. [c] • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Mosunetuzumab, tiragolumab, and atezolizumab (if applicable) may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before mosunetuzumab, tiragolumab, and atezolizumab (if applicable) can be resumed.

[c] Resumption of mosunetuzumab, tiragolumab, and atezolizumab (if applicable) may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with study treatment should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

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Appendix 7
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.

Appendix 8
Schedule of Assessments for Tocilizumab Treatment of CRS

Table A8-1 Schedule of Assessments for Tocilizumab Treatment of CRS: First Tocilizumab Dose

Assessment [a] / Procedure	Pre-TCZ Tx (within 24 hours)	TCZ Admin	Post-TCZ Treatment					
			6 h (±3 h)	24 h (±4 h)	48 h (±4 h)	72 h (±4 h)	8 days/ 192 h (±48 h)	8 weeks [b]
TCZ administration (8 mg/kg for participants ≥30 kg; 12 mg/kg for participants <30 kg) Doses exceeding 800 mg per infusion are not recommended.		x						
Vital signs [c]	x [d]		Measure at least every 6 hours until resolution to baseline, then every 12 hours until end of hospitalization [d]					
Pressor documentation [e]	x [d]		Record at least every 6 hours until pressors are discontinued [d]					
FiO_2	x [d]		Record at least every 6 hours until participant on room air [d]					
Pulse oximetry, resting	x [d]		Measure at least every 6 hours until resolution to baseline, and then every 12 hours until end of hospitalization [d]					
Local Laboratory Assessments								
Hematology	x		x	x	x	x	x	
Liver function tests (AST, ALT, total bilirubin)	x		x	x	x	x	x	

Table A8-1 Schedule of Assessments for Tocilizumab Treatment of CRS: First Tocilizumab Dose (cont.)

Assessment [a] / Procedure	Pre-TCZ Tx (within 24 hours)	TCZ Admin	Post-TCZ Treatment					
			6 h (±3 h)	24 h (±4 h)	48 h (±4 h)	72 h (±4 h)	8 days/ 192 h (±48 h)	8 weeks [b]
Serum chemistry and creatinine [f]	x		x	x	x	x	x	
CRP, LDH, and serum ferritin	x		x	x	x	x	x	
Coagulation (aPTT, PT or INR, fibrinogen)	x		x	x	x	x	x	
Infection work-up [g]	x							

Table A8-1 Schedule of Assessments for Tocilizumab Treatment of CRS: First Tocilizumab Dose (cont.)

Admin=administration; CRP=C-reactive protein; Discon.=discontinuation; EBV=Epstein-Barr virus; eCRF=electronic Case Report Form; IL-6=interleukin 6; PBMC=peripheral blood mononuclear cells; TCZ=tocilizumab; Tx=treatment.

Note: Record abnormalities or worsened clinically significant abnormalities on the Adverse Event eCRF.

[a] If a participant is hospitalized at a facility that does not have the capacity to perform a study assessment, the Medical Monitor should be notified. Hospitalization should not be prolonged to perform study assessments in this schedule of activities. Note this schedule of assessments applies to participants receiving their first dose of tocilizumab. For subsequent doses, see Table A8-2.

[b] Sample should be collected approximately 8 weeks (±14 days) after the last dose of tocilizumab.

[c] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated or supine position, and temperature.

[d] The maximum and minimum values for any 24-hour period should be recorded in the clinical database.

[e] Document vasopressor name and dose in the concomitant medication eCRF.

[f] Includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, and BUN or urea.

[g] Evaluate for bacterial, fungal, and viral infections using cultures, serologies, and molecular diagnostic tests as clinically indicated based on the individual participant's status and local practice for febrile oncology participants. At minimum, blood cultures should be obtained.

Table A8-2 Schedule of Assessments for Tocilizumab Treatment of CRS: Second, Third, or Fourth Dose

Assessment [a] / Procedure	Pre-TCZ Tx (within 24 hours)	TCZ Admin	Post-TCZ Treatment		
			Within 15 minutes after the end of TCZ Infusion	24 h (±4 h)	8 weeks [g]
TCZ administration (8 mg/kg for participants ≥30 kg; 12 mg/kg for participants < 30 kg) Doses exceeding 800 mg per infusion are not recommended.		x			
Vital signs [b]	x [c]		Measure at least every 6 hours until resolution to baseline, then every 12 hours until end of hospitalization [c]		
Pressor documentation [d]	x [c]		Record at least every 6 hours until pressors are discontinued [c]		
FiO_2	x [c]		Record at least every 6 hours until participant on room air [c]		
Pulse oximetry, resting	x [c]		Measure at least every 6 hours until resolution to baseline, and then every 12 hours until end of hospitalization [c]		
Local Laboratory Assessments					
Hematology	x				
Liver function tests (AST, ALT, total bilirubin)	x				
Serum chemistry and creatinine [e]	x				
CRP, LDH, and serum ferritin	x				
Coagulation (aPTT, PT or INR, fibrinogen)	x				
Infection work-up [f]	x				

Table A8-2 Schedule of Assessments for Tocilizumab Treatment of CRS: Second, Third, or Fourth Dose (cont.)

Admin = administration; CRP = C-reactive protein; EBV = Epstein-Barr virus; eCRF = electronic Case Report Form; IL-6 = interleukin 6; PBMC = peripheral blood mononuclear cells; TCZ = tocilizumab; Tx = treatment.

Note: Record abnormalities or worsened clinically significant abnormalities on the Adverse Event eCRF.

[a] If a participant is hospitalized at a facility that does not have the capacity to perform a study assessment, the Medical Monitor should be notified. Hospitalization should not be prolonged to perform study assessments in this schedule of activities.

[b] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated or supine position, and temperature.

[c] The maximum and minimum values for any 24-hour period should be recorded in the clinical database.

[d] Document vasopressor name and dose in the concomitant medication eCRF.

[e] Includes sodium, potassium, chloride, bicarbonate, glucose, and BUN.

[f] Evaluate for bacterial, fungal, and viral infections using cultures, serologies, and molecular diagnostic tests as clinically indicated based on the individual participant's status and local practice for febrile oncology participants. At minimum, blood cultures should be obtained.

[g] Sample should be collected approximately 8 weeks (± 14 days) after the last dose of tocilizumab.

Appendix 9
American Society for Transplantation and Cellular Therapy Cytokine Release Syndrome Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5[d]
Fever[a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	
			with		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)	
			and/or[b]		
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., C-PAP, BiPAP, intubation, and mechanical ventilation)	
					Death

BiPAP = bilevel positive airway pressure; C-PAP = continuous positive airway pressure; CRS = cytokine release syndrome; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Note: Organ toxicities associated with CRS may be graded according to NCI CTCAE v5.0 but they do not influence CRS grading.

[a] Fever is defined as a temperature ≥38°C not attributable to any other cause. In participants who have CRS and then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is determined by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event, hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5°C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. A high-low nasal cannula is defined as oxygen delivered at >6 L/min.

[d] Grade 5 CRS is defined as death due to CRS.

Appendix 10
2014 Lugano Response Criteria for Malignant Lymphoma

Response should be determined on the basis of radiographic and clinical evidence of disease. Assessment of the positron emission tomography/computed tomography (PET/CT) scan should follow the criteria presented below (Cheson et al. 2014). Contrast-enhanced CT is preferred for more precise measurements of nodal masses and differentiation between normal anatomy and disease nodal infiltration of mediastinum and abdominal cavity.

TARGET AND NON-TARGET LESIONS

Up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters should be identified from different body regions representative of the participant's overall disease burden and include mediastinal and retroperitoneal disease, if involved. At baseline, a measurable node must be > 15 mm in the longest diameter (LDi). Measurable extranodal disease may be included in the six representative, measured lesions. At baseline, measurable extranodal lesions should be greater than 10 mm LDi.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-measured disease as non-target lesions (e.g., cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, bone marrow).

SPLEEN INVOLVEMENT

Spleen may be of normal size or enlarged, homogeneous splenomegaly, or diffuse infiltration with small lesions or large solid mass.

A single measurement that correlates well with volume is preferable and the cut off > 13 cm in the vertical length for splenomegaly is recommended.

LIVER INVOLVEMENT

Measurement of liver size is not reliable by CT. Liver involvement is similar to the spleen involvement as diffuse increased or focal uptake on PET, with or without focal lesions.

BONE MARROW INVOLVEMENT

If applicable, bone marrow involvement uptake in PET is scored using the 5-point scale as nodal sites.

SPLIT LESIONS AND CONFLUENT LESIONS

Lesions may split or may become confluent over time. In the case of split lesions, the individual product of the perpendicular diameters (PPDs) of the nodes should be

summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression. In the case of confluent lesions, the PPD of the confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and smallest diameter (SDi) are no longer needed to determine progression.

Appendix 10: 2014 Lugano Response Criteria for Malignant Lymphoma

Revised Criteria for Response Assessment		
Response and Site	PET/CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra-lymphatic sites	Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b] It is recognized that in Waldeyer ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony–stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial response	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extra-lymphatic sites	Score 4 or 5 b with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5×5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, assign 0×0 mm as the default value For a node >5×5 mm but smaller than normal, use actual measurement for calculation

Revised Criteria for Response Assessment (cont.)		
Response and Site	PET/CT-Based Response	CT-Based Response
Non-measured lesion	Not applicable	Absent or 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
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least one of the following:
Individual target nodes/nodal masses	Score 4 or 5 b with an increase in intensity of uptake from baseline and/ or new FDG-avid foci	PPD progression

Revised Criteria for Response Assessment (cont.)		
Response and Site	PET/CT-Based Response	CT-Based Response
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 (> 13 cm), 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 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisting non-measured 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

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

[a] A score of 3 in many participants indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in study involving PET in which 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), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: any disease not selected as measured; dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., gastrointestinal 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).

[b] PET 5PS: 1=no uptake above background; 2=uptake >mediastinum; 3=uptake >mediastinum but ≤liver; 4=uptake moderately >liver; 5=uptake markedly higher than liver and/or new lesions; X =new areas of uptake unlikely to be related to lymphoma.

REFERENCES

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;3:3059-68.

Appendix 11
Eastern Cooperative Oncology Group Performance Status Scale

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

Source: Oken et al. 1982.

REFERENCES

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.

Appendix 12
Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes [a]	Sensitive Substrates [b]	Substrates with Narrow Therapeutic Range [c]
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine	Theophylline, tizanidine
CYP2B6 [d]	Bupropion	
CYP2C8	Repaglinide [e]	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Omeprazole, S-mephenytoin	S-mephenytoin
CYP3A [f]	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	Alfentanil, astemizole [g], cisapride [g], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [g]
CYP2D6	Atomoxetine, desipramine, dextromethorphan , eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine	Thioridazine

AUC = area under the concentration-time curve; CYP = cytochrome P450 enzymes.

[a] Note that this is not an exhaustive list. For an updated list, see the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

[b] Sensitive CYP substrates refer to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[c] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., torsades de pointes).

[d] The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

[e] Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.

[f] Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of Pgp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.

[g] Withdrawn from the U.S. market because of safety reason.

SAMPLE LIST OF CAUTIONARY MEDICATIONS

(A) INHIBITORS

	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP3A	Boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,[a] indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole	Aprepitant, ciprofloxacin, conivaptan, crizotinib,[a] cyclosporine,[a] diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, [a] tofisopam, verapamil	Chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, ticagrelor

[a] These are the anti-cancer agents; contact Medical Monitor before use.

(B) INDUCERS

	Strong Inducers	Moderate Inducers	Weak Inducers
CYP3A	Avasimibe, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, phenobarbital, primidone	Armodafinil, modafinil, rufinamide

REFERENCES

U.S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers [resource on the Internet]. 2017 [cited 4 Feb 2021]. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

Appendix 13
Preexisting Autoimmune Diseases and Immune Deficiencies

Participants should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Participants with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be participants with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. See Section 5.2 or additional exceptions. Caution should be used when considering study treatment for participants who have previously experienced a severe or life-threatening skin adverse reaction *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

AUTOIMMUNE DISEASES AND IMMUNE DEFICIENCIES

- Acute disseminated encephalomyelitis
- Addison disease
- Ankylosing spondylitis
- Anti-phospholipid antibody syndrome
- Aplastic anemia
- Autoimmune hemolytic anemia
- Autoimmune hepatitis
- Autoimmune hypoparathyroidism
- Autoimmune hypophysitis
- Autoimmune *myelitis*
- *Autoimmune* myocarditis
- Autoimmune oophoritis
- Autoimmune orchitis
- Autoimmune thrombocytopenic purpura
- Behçet disease
- Bullous pemphigoid
- Chronic fatigue syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Churg-Strauss syndrome
- Crohn disease
- Dermatomyositis
- Diabetes mellitus type 1
- Dysautonomia
- Epidermolysis bullosa acquisita
- Gestational pemphigoid
- Giant cell arteritis
- Goodpasture syndrome
- Graves disease
- *Granulomatosis with polyangiitis*
- Guillain-Barré syndrome
- Hashimoto disease
- IgA nephropathy
- Inflammatory bowel disease
- Interstitial cystitis
- Kawasaki disease
- Lambert-Eaton myasthenia syndrome
- Lupus erythematosus
- Lyme disease, chronic
- Meniere syndrome
- Mooren ulcer
- Morphea
- Multiple sclerosis
- Myasthenia gravis Neuromyotonia
- Opsoclonus myoclonus syndrome
- Optic neuritis
- Ord thyroiditis
- Pemphigus
- Pernicious anemia
- Polyarteritis nodosa
- Polyarthritis
- Polyglandular autoimmune syndrome
- Primary biliary cholangitis
- Psoriasis
- Reiter syndrome
- Rheumatoid arthritis
- Sarcoidosis
- Scleroderma
- Sjögren syndrome
- Stiff-Person syndrome
- Takayasu arteritis
- Ulcerative colitis
- Vitiligo
- Vogt-Koyanagi-Harada disease

Appendix 14
Abbreviations

Abbreviation or Term	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
aLugano	automated response using Lugano 2014 criteria
ASTCT	American Society for Transplantation and Cellular Therapy
aTMTV	automated total metabolic tumor volume
AUC	area under the concentration–time curve
BR	bendamustine and rituximab
C#D# (e.g., C1D1)	Cycle # Day # (e.g., Cycle 1 Day 1)
CAR	chimeric antigen receptor
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events, Version 5.0
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicities
EBV	Epstein-Barr virus
EC	ethics committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
FDA	(U.S.) Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed, paraffin-embedded
FL	follicular lymphoma
HBV	hepatitis B virus
HCV	hepatitis C virus
HGBL	high grade B-cell lymphomas
HLH	hemophagocytic lymphohistiocytosis
ICI	immune checkpoint inhibitor
IFN	interferon

Appendix 14: Abbreviations

Abbreviation or Term	Definition
IL	interleukin
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
MAS	macrophage activation syndrome
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer
NOS	not otherwise specified
OS	overall survival
PBMC	peripheral blood mononuclear cell
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PRA	primary response assessment
PRO	participant-reported outcome
Q3W	every 3 weeks
QTcF	QT interval corrected through use of Fridericia's formula
PI3K	phosphoinositide 3–kinase
R/R	relapsed/refractory
RBR	Research Biosample Repository
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy of Cancer
TIGIT	T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine based inhibition motif domains
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
trFL	transformed follicular lymphoma
ULN	upper limit of normal
USPI	United States Prescribing Information
WES	whole exome sequencing

Appendix 14: Abbreviations

Abbreviation or Term	Definition
WGS	whole genome sequencing

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