CLINICAL STUDY PROTOCOL

A Phase 2 Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of XmAb®13676 (Plamotamab) Combined with Tafasitamab Plus Lenalidomide Versus Tafasitamab Plus Lenalidomide in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Protocol No.:	XmAb13676-03
IND No.:	IND 129984
EudraCT:	Pending
Test Product:	XmAb®13676 (Plamotamab)
Indication:	Relapsed-refractory diffuse large B-cell lymphoma (R/R DLBCL)
Sponsor:	Xencor, Inc. 111 West Lemon Avenue Monrovia, CA 91016 Telephone: [redacted]
Development Phase:	Phase 2
Sponsor Medical Expert:	[redacted] Xencor, Inc. Telephone: [redacted] E-mail: [redacted]
Version and Date:	Version 2.0 (08 March 2022)
Replaces Version and Date:	Version 1.0 (15 December 2021)

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and applicable Independent Ethics Committee and/or Institutional Review Board. It is understood that the information will not be disclosed to others without written authorization from Xencor, Inc. except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Expert

PROTOCOL TITLE: A Phase 2 Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of XmAb®13676 (Plamotamab) Combined with Tafasitamab Plus Lenalidomide Versus Tafasitamab Plus Lenalidomide in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

PROTOCOL NUMBER: XmAb13676-03

Xencor, Inc.

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 2013), and the current guidelines on Good Clinical Practices (GCP) applicable to this clinical study.

{See appended electronic signature at the end of the document}

[redacted]
Xencor, Inc.

INVESTIGATOR PROTOCOL SIGNATURE PAGE

Protocol No. XmAb13676-03 (Version 2.0)

A Phase 2 Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of XmAb®13676 (Plamotamab) Combined with Tafasitamab Plus Lenalidomide Versus Tafasitamab Plus Lenalidomide in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

08 March 2022

I have read and understand the protocol and the Investigator's Brochure, and I agree that they contain all the ethical, legal, and scientific information necessary to conduct this study. I will conduct this protocol as outlined herein and will make every effort to complete the study within the time designated.

I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

The protocol may not be modified without written approval of the Sponsor. All changes to the protocol must be submitted to the applicable regulatory authorities, Institutional Review Board (IRB), and Independent Ethics Committee (IEC) and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the Sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the Sponsor immediately upon receipt.

By my signature below, I hereby attest that I have read, understood, and agreed to abide by all the conditions, instructions, and restrictions contained in Protocol XmAb13676-03 and in accordance with International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines, the Declaration of Helsinki, and all regulatory requirements for protection of human subjects in clinical studies and privacy requirements for the protection of individual and company data.

I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interest of the study subjects.

_____
Printed Name of Principal Investigator

_____
Signature of Principal Investigator

_____
Date

LIST OF STUDY STAFF/EMERGENCY CONTACTS

Sponsor:	Xencor, Inc. 111 West Lemon Avenue Monrovia, CA. 91016 Telephone: [redacted]
Medical Monitor:	[redacted] Xencor, Inc. Telephone: [redacted] E-mail: [redacted]
Serious Adverse Event Reporting:	ICON PVSS E-mail: [redacted] Fax number: [redacted] Emergency phone number: [redacted] (toll free within US) or [redacted] (toll number) Back-up number: [redacted]
Contract Research Organization:	ICON Clinical Research Ltd South County Business Park Leopardstown, Dublin 18 Ireland
Bioanalytical Laboratory (Pharmacokinetics, Anti-Drug Antibodies, Cytokine Assays):	See Laboratory Manual for contact information.
Bioanalytical Laboratory (Flow Cytometry, Immunohistochemistry, and Biobanking):	See Laboratory Manual for contact information.

SYNOPSIS

Name of Sponsor/Company:

Xencor, Inc.

111 West Lemon Avenue

Monrovia CA 91016

Name of Investigational Product:

XmAb®13676 (plamotamab)

Name of Active Ingredient:

XmAb®13676

Title of Study:

A Phase 2 Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of XmAb®13676 (Plamotamab) Combined with Tafasitamab Plus Lenalidomide Versus Tafasitamab Plus Lenalidomide in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Study Period:	**Phase of Development:** 2
Estimated date first subject enrolled: Quarter 1 2022	
Estimated date last subject completed: Quarter 4 2027	

Objectives:

Primary Objectives:

The primary objective of the study is to:

Determine the safety and efficacy of the combination of plamotamab, tafasitamab, and lenalidomide compared to tafasitamab and lenalidomide in adult subjects with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL).

Secondary Objectives:

The secondary objectives of the study are to compare the combination of plamotamab, tafasitamab, and lenalidomide to tafasitamab and lenalidomide for the following assessments:

1. Rates of objective response (ORR = CRR + partial response rate [PRR]) by Blinded Independent Review Committee (BIRC) and Investigator per Lugano 2014 criteria
2. Overall survival (OS)
3. Time to treatment failure (TTF)
4. Duration of response (DOR) among subjects achieving an objective response (CR + PR) and among subjects achieving a complete response (CR) by BIRC
5. Progression-free survival (PFS), as determined by the Investigator
6. Incidence, timing, and severity of cytokine release syndrome (CRS) by following CRS-related adverse events (AEs) including incidence and grade of AEs and incidence of serious adverse events (SAEs)

7. Incidence, timing, and severity of neurological AEs and incidence and grade of immune effector cell-associated neurotoxicity syndrome
8. Dose intensity of tafasitamab and lenalidomide in Part 1 when given in combination with plamotamab
9. Safety profile of the combination of plamotamab, tafasitamab, and lenalidomide in Part 2, as determined by the incidence and severity of treatment-emergent adverse events (TEAEs), in adult subjects with R/R DLBCL

Study Endpoints:

Primary Efficacy Endpoints:

The primary endpoints for each part of the study are:

- For Part 1, safety as measured by incidence of CRS and TEAEs; and
- For Part 2, PFS, defined as the time from randomization to first documentation of progressive disease or death, whichever comes first, as assessed by the BIRC using Lugano 2014 criteria.

Secondary Endpoints:

The secondary endpoints of the study are as follows:

1. Best objective response rate (ORR) and CRR, as assessed by Investigator and by the BIRC according to Lugano 2014 criteria
2. OS, defined as the time from randomization to death from any cause
3. TTF, defined as the time from randomization to discontinuation of all study treatment for any reason, including disease progression (as assessed by Investigator and by BIRC), treatment toxicity, and death, whichever comes first
4. DOR, defined as the time from first response to progression or death due to any cause, whichever comes first, among subjects achieving an objective response (OR) and among subjects with complete response (CR) as assessed by BIRC
5. Progression-free survival (PFS), as assessed by Investigator using Lugano 2014 criteria
6. Incidence, timing, and severity of CRS as assessed by following CRS-related AEs, including incidence and grade of AEs and incidence of SAEs, with CRS grading defined by the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading
7. Incidence, timing, and severity of neurological AEs, and incidence and grade of immune effector cell-associated neurotoxicity syndrome
8. Dose intensity of tafasitamab and lenalidomide as measured by planned and actual dose administration in Part 1
9. Incidence and severity of TEAEs in Part 2, with severity defined by National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Methodology:

This is a randomized, multicenter, open-label, Phase 2 study of plamotamab combined with tafasitamab plus lenalidomide versus tafasitamab plus lenalidomide in adult subjects with DLBCL who have relapsed after or are refractory to at least 1 prior line of therapy, which must have included multi-agent chemoimmunotherapy inclusive of an anti-CD20 monoclonal antibody, and who are not candidates for ASCT, refuse ASCT, or relapse after ASCT.

The study will consist of 2 parts. Part 1 will enroll and evaluate subjects in 2 cohorts (A and B) for safety and determination of dose and dose schedule. After dosing has been determined, Part 2, with 2 arms (A and B), will begin.

Part 1 is a single-arm evaluation of the safety of the triple combination of plamotamab combined with tafasitamab plus lenalidomide in at least 40 subjects, in 2 cohorts of a minimum of 20 subjects per cohort.

Part 1, Cohorts 1A and 1B:

- Cohort 1A treats subjects with the triple combination at plamotamab dose level – 1.
- Cohort 1B enrollment starts after Cohort 1A completes enrollment. Cohort 1B treats subjects with the triple combination at plamotamab dose level 1.
- An initial safety evaluation is conducted after all subjects in Cohorts 1A and 1B either receive treatment, at a minimum, through C4D28 or are discontinued prior to C4D28 due to an AE or progressive disease.

Part 2 is open-label and randomized and begins after an initial safety evaluation of at least 40 subjects from Part 1, Cohorts 1A and 1B, after which the pharmacologically optimal dose of plamotamab (dose level – 1 or dose level 1) with an acceptable safety profile will be advanced to the randomized (Part 2) portion of the study. Prior to the initiation of Part 2, this protocol will be revised with the dosing regimen selected from Part 1 and will include adequate justification to support the proposed dose/schedule in Part 2.

During Part 2, subjects are randomized in a 1:1 ratio to the 2 treatment arms, stratified by international prognostic index (IPI) risk score at baseline (3 to 5 versus 0 to 2), number of lines of prior therapy (1 versus ≥ 2), and primary refractory (yes versus no). Primary refractory enrollment is limited to 36 of 200 subjects. Part 2 will enroll approximately 200 subjects. The sample size for Part 2 may be adjusted based on the results from Part 1. An increase in the enrollment number beyond 200 will be made by a protocol amendment prior to the initiation of the randomized portion. An independent data monitoring committee (IDMC) will review safety data during Part 2 with meetings scheduled after 50, 100, and 150 subjects have been randomized. The primary analysis for PFS will occur after 89 disease progression and death events. An interim analysis for OS will also be performed at that time.

All subjects will be treated until progression or withdrawal for other reasons and then followed for OS for up to 5 years.

Of note: A central pathologist reading will confirm the diagnosis of DLBCL retrospectively after enrollment, using archival or recently obtained tissue. Central radiology and clinical reviewers will assess objective disease response according to the Lugano 2014 guidelines. Details of the central review will be provided in an imaging charter outlining functions and processes. In addition, Investigator-assessed response will be captured in the clinical database, and concordance analyses will be performed.

Number of Subjects (planned):
Part 1 will enroll at least 40 subjects into 2 cohorts (1A, 1B) with a minimum of 20 subjects per cohort.

Part 2 will enroll approximately 200 subjects in 2 arms, A and B. The sample size for Part 2 may be adjusted based on the results from Part 1. Any increase in the enrollment number beyond 200 will be made by a protocol amendment prior to the initiation of the randomized portion. Primary refractory enrollment will be limited in Part 2 to 36 of 200 subjects.

Total number of subjects planned for the entire study is approximately 240 subjects. *Of note:* Treatment assignment for Part 1 and randomization for Part 2 will be performed via third-party randomization and trial supply management (RTSM)/interactive response technology (IRT) system.

Number of Clinical Investigational Sites (planned): Up to 120 in the United States and outside the United States

Inclusion Criteria:

To be eligible for enrollment, subjects must meet all the following criteria:

- Adult (age ≥ 18 years)
- Able to provide written informed consent
- Histologically confirmed diagnosis of DLBCL, not otherwise specified (NOS), including DLBCL arising from low-grade lymphoma (ie, an indolent pathology such as follicular lymphoma, or marginal zone lymphoma transforming into DLBCL)
- Subjects must have CD20+ and CD19+ lymphoma based on flow cytometric or immunohistochemical evaluation of their most recent biopsy
- At a minimum, archival paraffin embedded tumor tissue (preferred) or unstained slides must be available for retrospective cell of origin determination by a central independent pathologist. Subjects will be consented and may undergo an optional (recommended) biopsy to obtain fresh tumor tissue if a peripheral disease site can easily and safely be accessed. A fresh tumor tissue sample will satisfy this criterion for those subjects who do not have adequate archival tumor tissue; in this case, the fresh tumor biopsy becomes mandatory for participation.
- Subjects must have at least 1 of the following:
  - Relapsed disease after standard therapeutic options, as defined below:
    - Documented progressive disease (PD), according to the Lugano 2014 criteria after the most recently administered anti-lymphoma regimen
  - Primary refractory DLBCL, defined as follows:
    - Documented persistent disease (less than a complete remission [PR, SD, or PD], according to the Lugano 2014 criteria) at the completion of first-line therapy, or
    - PD (according to the Lugano 2014 criteria) within 3 months of completion of first-line therapy
- Subjects must have received at least 1 prior systemic line(s) of therapy, one of which must have included multi-agent chemoimmunotherapy that includes an anti-CD20 monoclonal antibody. DLBCL arising from low-grade lymphoma must have relapsed or refractory disease after at least 2 prior lines of chemoimmunotherapy (at least one of which must have been directed at the DLBCL arising from low grade lymphoma).
- At least 1 bidimensionally measurable disease site. The lesion must have a greatest transverse diameter of ≥ 1.5 cm and greatest perpendicular diameter of ≥ 1.0 cm at baseline. The lesion must have a positive finding on PET scan.
- Subjects who are ineligible for or refuse hematopoietic stem cell transplantation (HSCT). Subjects may be considered ineligible for HSCT for any of the following reasons (Documentation of the reason for a subject's ineligibility must be provided in the subject's source data and eCRF):
  - Age
  - Performance status
  - Comorbidities

  - Stem cell mobilization failure
  - Failure of prior transplant
  - Insufficient response to salvage chemotherapy
  - Subject refusal
  - Logistical reasons
  - Other potential reasons not listed above will be considered on a case-by-case basis
- If eligible for chimeric antigen receptor-T cell (CAR-T) therapy, subjects must consent to bypassing the approved treatment with demonstrated clinical benefit
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
- Completed vaccination for the SARS-CoV-2 virus prior to study entry is recommended

Laboratory Values

- Subjects must meet the following laboratory criteria at screening:
  - ANC $\geq 1.5 \times 10^9$/L (for subject with bone marrow involvement ANC $\geq 0.5 \times 10^9$/L)
  - Platelet count $\geq 90 \times 10^9$/L (for subjects with bone marrow involvement platelet count $\geq 50 \times 10^9$/L)
  - Total serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Subjects with Gilbert's syndrome or documented liver involvement by lymphoma may be included if their total bilirubin is $\leq 5 \times$ ULN
  - ALT, AST, and alkaline phosphatase $\leq 3 \times$ ULN, or $< 5 \times$ ULN in cases of documented liver involvement
  - Serum creatinine clearance must be $\geq$ 60 mL/minute calculated using a standard Cockcroft and Gault formula or Modification of Diet in Renal Disease (MDRD)
- Willingness to avoid pregnancy or fathering children based on the criteria below.
  - Male subjects with reproductive potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 180 days (6 months) after the last dose of study treatment, even if they have undergone a successful vasectomy, and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see section "Avoidance of Pregnancy") should be communicated to the subjects and their understanding confirmed.
  - Women of childbearing potential subjects:
    - Must commit either to abstain continuously from heterosexual sexual intercourse or agree to take appropriate precautions to avoid pregnancy (by using 2 different methods of birth control with at least 99% certainty) starting at least 4 weeks before taking the study treatment, while taking the study treatment, during breaks (dose interruptions), and for at least 8 months after stopping the study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see section "Avoidance of Pregnancy") should be communicated to the subjects and their understanding confirmed.

- Must have a negative serum pregnancy test at screening (within 10 to 14 days of Day –8) and before the first dose of lenalidomide on Day 1 (within 24 hours of initiating treatment with lenalidomide).
- Agree to ongoing pregnancy testing during the course of the study: weekly during the first month of study drug treatment, then monthly thereafter for women with regular menstrual cycles or every 2 weeks for women with irregular menstrual cycles (even if true abstinence is the chosen method of birth control) up to and including the end-of-treatment (EOT) visit.
- Must refrain from breastfeeding and donating oocytes during the course of study and for 8 months after the last dose of study treatment.

Note: The subjects should be informed about the option of donation and cryopreservation of germ cells before the study, if applicable.

- In the opinion of the Investigator, the subjects must:
  - Be able and willing to receive adequate prophylaxis and/or therapy for thromboembolic events
  - Be able to understand, give written informed consent, and comply with all study-related procedures, medication use, and evaluations
  - Not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative
  - Be able to understand the reason for complying with the special conditions of the protocol and supplemental Summary of Pregnancy Prevention Strategies and give written acknowledgement of this in the informed consent form (ICF)

Subject Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from the study.

Exclusionary Diagnosis

- High-grade B-cell lymphoma, including those with MYC and BCL2 and/or BCL6 rearrangements (double-hit or triple-hit lymphoma) and high grade B-cell lymphoma NOS, according to WHO 2016 criteria.
- Any other histological type of lymphoma, including primary mediastinal (thymic) large B-cell (PMBL) or Burkitt lymphoma
- A prior diagnosis of chronic lymphocytic leukemia (CLL) (Richter's Transformation)
- Primary central nervous system (CNS) lymphoma
- A history of secondary CNS involvement by DLBCL are ineligible, unless treated into remission

Exclusionary Previous and Current Treatment

- Subjects who have previously received treatment with an anti-CD20 × anti-CD3 bsAb
- Subjects who have been previously treated with tafasitamab
- Anti-CD20 therapy (eg, rituximab) within 21 days prior to Day –8, to minimize competition with plamotamab binding to CD20 on DLBCL target cells
- Subjects who have, within 14 days prior to Day –8:

  - Chemotherapy, radiotherapy, or other lymphoma-specific therapy not including anti-CD20 therapy. Note: palliative local radiotherapy is permitted; however, these lesions may not serve as target lesions.
  - Small molecule or investigational anticancer agents within 6 elimination half-lives prior to Day –8
  - Undergone major surgery not related to lymphoma complications or suffered from significant traumatic injury
  - Received live vaccines within 30 days of Day –8
  - Required systemic anti-infective therapy for active, intercurrent infections
- Subjects who have had the following prior therapies or treatments:
  - Have, in the opinion of the Investigator, not recovered sufficiently from the adverse effects of prior therapy(ies)
  - Were previously treated with CD19-targeted therapy, including CAR-T, unless current biopsy (after last therapy) is CD19+
  - Have known intolerance to CD20 monoclonal antibody therapy
  - Have a history of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, immunomodulatory imide drugs (IMiDs), and/or the excipients contained in the study drug formulations
  - Have undergone autologous stem cell transplantation (ASCT) ≤ 1 month prior to signing the informed consent form. Subjects who have a more distant history of ASCT must exhibit full hematologic recovery before enrollment into the study.
  - Have undergone previous allogenic stem cell transplantation
  - Have a history of deep venous thrombosis/embolism, threatening thromboembolism, or known thrombophilia, or are at high risk for a thromboembolic event in the opinion of the Investigator, and who are not willing/able to take venous thromboembolic event prophylaxis during the entire treatment period
  - Concurrently use other anticancer or experimental treatments

Exclusionary Subject's Medical History

- Prior history of malignancies other than DLBCL, unless the subject has been free of the disease for ≥ 3 years prior to screening. Exceptions to the ≥ 3-year time limit include a history of the following:
  - Basal cell carcinoma of the skin
  - Squamous cell carcinoma of the skin
  - Carcinoma in situ of the cervix
  - Carcinoma in situ of the breast
  - Carcinoma in situ of the bladder
  - Tumor/Node/Metastasis [TNM] stage of T1a or T1b prostate cancer
- Subjects with the following medical history:

- Known active hepatitis infection:
  - Positive test for HBsAg or HBcAb (a subject whose HBsAg or HBcAb is positive may be enrolled if an HBV DNA test is negative and either the subject is treated with potent antiviral therapy or is re-tested for HBV DNA every month)
  - Positive test for HCV antibodies (a subject whose HCV antibody test is positive may be enrolled if quantitative HCV polymerase chain reaction test is negative)
- Known seropositivity for or history of active viral infection with HIV
- Positive SARS-CoV-2 nucleic acid or antigen test
- History or evidence of clinically significant cardiovascular, CNS, and/or other systemic disease that would in the Investigator's opinion preclude participation in the study or compromise the subject's ability to give informed consent
- History of solid organ transplantation
- History or evidence of rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
- Gastrointestinal abnormalities that would interfere with the ability to take or absorb oral medication

Dose, Route of Administration, and Treatment Regimen

Study Drugs:
Three study drugs are in use during this study: 1) Xencor study drug product DP /investigational medicinal product (IMP), plamotamab, and 2 other drugs previously approved by the FDA, 2) tafasitamab -cxix and 3) lenalidomide. The drugs will be used in triple combination, plamotamab (+) tafasitamab (+) lenalidomide.

1) Plamotamab (XmAb13676) is a humanized bsAb that binds both CD3 and the tumor antigen CD20 in order to recruit cytotoxic T cells to kill CD20 positive tumor cells. IV Solution Stabilizer (IVSS) is a concentrated form of the plamotamab (XmAb13676) buffer that also minimizes protein binding to the administration equipment when plamotamab is administered at lower concentrations.
2) Tafasitamab (tafasitamab-cxix) is a CD19-directed cytolytic antibody indicated for use in the US in combination with lenalidomide for the treatment of adult patients with R/R DLBCL not otherwise specified (NOS), including DLBCL arising from low-grade lymphoma, and who are not eligible for ASCT.
3) Lenalidomide, a thalidomide analogue, is an immunomodulatory agent (IMiD®) with antiangiogenic and antineoplastic properties. It is indicated for the treatment of adult patients with multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma, follicular lymphoma, and marginal zone lymphoma.

Study Drug Dose Administration and Regimen:

Plamotamab (XmAb13676) – Subjects in Part 1 and those randomized to Arm A in Part 2 will be administered plamotamab IV [redacted]
In Cycle 1, plamotamab will be administered once every 7 days (± 1 day) for 4 doses; beginning with Cycle 2, plamotamab will be administered every 2 weeks (Q2W). Doses of plamotamab anticipated for use during the study via IV infusions include: 0.8 mg, 2 mg, and 20 mg. Refer to dosing table below.

Tafasitamab and plamotamab must not be administered simultaneously. On days when both tafasitamab and plamotamab are given, the tafasitamab should be given first followed by plamotamab. It is recommended that the infusions are separated by at least 2 hours.

Part 1, Cohort 1A and 1B, Plamotamab Dosing Regimen

Cohort	Dose Level	Cycle 1 Day 1 (Priming Dose)	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22	Cycle 2 Day 1	Cycle 2 Days 1, 8, 15, and 22	Cycle 3 and Subsequent Q2W Dosing
1A	–1	0.8 mg	2 mg	20 mg	20 mg	20 mg	20 mg	20 mg
1B	1	0.8 mg	2 mg	20 mg	35 mg	50 mg	50 mg	50 mg

Q2W= every 2 weeks.

Tafasitamab: All subjects will receive tafasitamab. Priming doses will be administered on Days –8 and –4 of a 1-week run-in period. During the first 3 cycles of the study, tafasitamab will be infused on Day 1, Day 8, Day 15, and Day 22 of each cycle. Thereafter, tafasitamab will be administered on a biweekly (every 14 days) basis, with infusions on Days 1 and 15 of each 28-day cycle until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first. Refer to dosing table below. Tafasitamab and plamotamab must not be administered simultaneously. On days when both tafasitamab and plamotamab are given, the tafasitamab should be given first followed by plamotamab. It is recommended that the infusions are separated by at least 2 hours.

Tafasitamab Dosing Regimen

Day –8 and –4 (Priming Dose)	Cycle 1 Days 1, 8, 15, 22	Cycle 2 Days 1, 8, 15, 22	Cycle 3 Days 1, 8, 15, 22	Cycle 4 and Subsequent Q2W Dosing
12 mg/kg	12 mg/kg	12 mg/kg	12 mg/kg	12 mg/kg

Q2W = every two weeks.

Lenalidomide: All subjects will receive lenalidomide and self-administer a starting dose of 25 mg oral lenalidomide daily on Days 1 to 21 of each cycle. No more than 21 doses of lenalidomide will be dispensed per cycle; lenalidomide can be given for only up to a total of 12 cycles. Investigators will follow the package insert or SmPC for recommended medications for venous thromboembolic event prophylaxis and dosing modifications. It is recommended that subjects take oral (PO) lenalidomide in the evening about the same time each day, with or without food. Subjects are to swallow lenalidomide capsules whole with water. When ingesting, the capsules should not be opened, broken, or chewed. Treatment with lenalidomide may be modified in a deescalating fashion or discontinued based upon clinical and laboratory findings. Detailed dose modification guidelines to manage hematologic and/or other toxicities are provided in the relevant sections of the protocol.

Study Drug Use in Part 1: Single-arm, Two-cohort, Safety Run-in

This first part of the study is designed to establish a dose of plamotamab with an acceptable safety profile when given in combination with the other 2 drugs.

- Part 1, Cohort 1A treats subjects with the triple combination at plamotamab dose level –1.
- Part 1, Cohort 1B commences enrollment after Cohort 1A completes enrollment. Cohort 1B treats subjects with the triple combination at plamotamab dose level 1.

- An initial safety evaluation is conducted after all subjects in Cohorts 1A and 1B either receive treatment, at a minimum, through C4D28 or are discontinued prior to C4D28 due to an AE or progressive disease.

Study Drug Use in Part 2: Two-Arm, Open-label, Randomized, Efficacy and Safety

After the initial safety evaluation of both Cohorts 1A and 1B, the pharmacologically optimal dose of plamotamab with an acceptable safety profile (dose level -1 or dose level 1) will be advanced to the randomized, Part 2, of the study. Subjects are randomized in a 1:1 ratio to 2 treatment arms, Arm A and Arm B. The subjects are stratified to one arm or the other by using 3 criteria: international prognostic index (IPI) risk score at baseline (3 to 5 versus 0 to 2), number of lines of prior therapy (1 versus ≥ 2), and primary refractory (yes versus no).

- Part 2: Arm A:

  Treatment consists of the combination of plamotamab, tafasitamab, and lenalidomide administered in 28-day cycles, with 2 priming doses of tafasitamab before Cycle 1. Plamotamab and tafasitamab can be administered until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first. Lenalidomide can be given for up to a total of 12 cycles.

- Part 2: Arm B:

  Treatment consists of the combination of tafasitamab and lenalidomide administered in 28-day cycles with 2 priming doses of tafasitamab before Cycle 1. Tafasitamab can be administered until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first. Lenalidomide can be given for up to a total of 12 cycles.

Duration of Treatment: Plamotamab and tafasitamab can be administered until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first; however, lenalidomide can be given for only up to a total of 12 cycles.

Primary Endpoint Assessment Criteria:

- For Part 1, safety as measured by incidence of CRS and TEAEs
  - TEAEs are defined as events with onset dates on or after the start of study treatment or events that are present before the first infusion of study treatment and subsequently worsen in severity.
  - AE-related endpoints include:
    - Treatment-emergent AEs
    - Treatment-emergent SAEs
    - Adverse reactions
    - Serious adverse reactions
    - Treatment-emergent AEs by severity, as defined by NCI-CTCAE Version 5.0
    - Treatment-emergent AEs resulting in the permanent discontinuation of plamotamab
    - Other safety variables include vital signs, PE findings, ECGs, laboratory values, medical history, and concomitant medications, which will be summarized by Part and by Arm.
- For Part 2, PFS, defined as the time from randomization to first documentation of progressive disease or death, whichever comes first, as assessed by the BIRC using Lugano 2014 criteria.

The following secondary endpoints will be tested sequentially in the following order, if the test for the primary endpoint is positive:

- ORR by BIRC per Lugano 2014 criteria
- OS
- TTF

Secondary Endpoint Assessment Criteria:

- Best ORR and CRR, as assessed by Investigator and by the BIRC according to Lugano 2014 criteria
- OS, defined as the time from randomization to death from any cause
- TTF, defined as the time from randomization to discontinuation of all study treatment for any reason, including disease progression (as assessed by Investigator and by BIRC), treatment toxicity, and death, whichever comes first
- DOR, defined as the time from first response to progression or death due to any cause, whichever comes first, among subjects achieving an objective response (OR) and among subjects with CR as assessed by BIRC
- PFS, as assessed by Investigator using Lugano 2014 criteria
- Incidence, timing, and severity of CRS as assessed by following CRS-related AEs, including incidence and grade of AEs and incidence of SAEs, with CRS grading defined by the ASTCT Consensus Grading
- Incidence, timing, and severity of neurological AEs, and incidence and grade of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
- Dose intensity of tafasitamab and lenalidomide as measured by planned and actual dose administration in Part 1
- Incidence and severity of TEAEs in Part 2, with severity defined by the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Statistical Methods and Data Analysis:

Efficacy Analysis

The Randomized (intent-to-treat) Analysis Set will be used for primary and secondary efficacy analyses, unless otherwise noted.

Efficacy analysis will utilize hazard ratio based on Cox regression model stratified by IPI risk score, number of lines of prior therapy, and primary refractory. KM estimates for median, Q1 and Q3. Stratified log-rank test for treatment effect.

PFS as assessed by the BIRC is the primary endpoint for Part 2 of this study. For determination of the sample size, it is assumed that triple combination treatment could improve the median PFS from 12 months (under treatment with tafasitamab + lenalidomide to 23.5 months under the triple combination treatment (plamotamab + tafasitamab + lenalidomide), corresponding to a hazard ratio (HR) of 0.51 with all randomized subjects (it is estimated that 90% of subjects will be central pathologically confirmed as DLBCL).

Safety Analysis

Safety Analysis will be performed with the Safety Analysis Set. All AE-related endpoints will be summarized by SOC and preferred term. At each level of summation, subjects will be counted once, under the greatest severity and strongest study-drug relationship.

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). The verbatim term recorded by the Investigator will be mapped to System Organ Class (SOC) and Preferred Term using MedDRA (MedDRA). Additional analysis will be performed for AEs of CRS. These will include analyses of time to onset, duration, severity, and associations with laboratory cytokine measurements and missed or delayed doses (ie, CRS may be associated with longer intervals between doses). Graphical summaries will illustrate the timing relative to dosing, the severity of CRS events and cytokine levels.

Vital sign results (blood pressure, heart rate, respirations, temperature, and blood oxygen saturation by continuous pulse oximetry) will be summarized descriptively for each scheduled time point.

The hematology, chemistry, and other laboratory values and change from baseline values will be summarized descriptively for each scheduled assessment time point and grouped by dosing cohort.

The toxicity grades for laboratory tests will be based on NCI-CTCAE Version 5.0 criteria.

The extent of exposure to plamotamab and tafasitamab will be summarized based on the number of infusions administered and the number of treatment cycles completed, as well as the total dose received. Lenalidomide exposure will be summarized similarly, based on number of doses taken.

Additional summaries of drug exposure will be provided based on the PK parameters described in the section "Pharmacokinetic Analysis."

Pharmacokinetic Analysis

Serum concentrations of plamotamab and tafasitamab will be listed, summarized in tabular form by dosing visit (including, mean, median, range, and 25^{th} and 75^{th} percentiles). Details of additional analyses will be provided in a PK analysis plan.

Immunogenicity Analysis

The incidence and titer of anti-plamotamab antibodies and anti-tafasitamab antibodies will be reported by sample collection time point and treatment arm, as applicable.

Biomarker Analyses

Biomarkers will be analyzed at the central laboratory per instruction in the Laboratory Manual and reported per the descriptions in the SAP. Exploratory endpoints will not be reported in the clinical study report. Serum cytokine levels will be reported using descriptive statistics and tabular display.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviations and Specialist Terms	Explanation
ABC	activated B cell
ADA	anti-drug antibodies
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
ASCT	autologous stem-cell transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
β-hCG	beta human chorionic gonadotropin
BIRC	Blinded Independent Review Committee
bsAb	bispecific antibody
CAR-T	chimeric antigen receptor-modified T-cell therapy
CBC	complete blood count
CI	confidence interval
CLL	chronic lymphocytic leukemia
COO	cell of origin assay
CNS	central nervous system
CR	complete response
CRS	cytokine release syndrome
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
C_{trough}	predose or trough concentration
DCF	Data Clarification Form
DICOM	Digital Imaging and Communications in Medicine
DLBCL	diffuse large cell B-cell lymphoma
DOR	duration of response
DP	drug product
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Abbreviations and Specialist Terms	Explanation
EDC	electronic data capture
EOI	end of infusion
EOS	end-of-study
EOT	end-of-treatment
FcγR	Fc gamma receptor
FDA	US Food and Drug Administration
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GCB	germinal center B-cell
GCP	good clinical practice
GGT	serum gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEENT	head, eyes, ears, neck, and throat
HIV	human immunodeficiency virus
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell-associated encephalopathy
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IL-6	interleukin-6
IMiD	immunomodulatory agent
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	international normalized ratio
IPI	international prognostic index
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system

Abbreviations and Specialist Terms	Explanation
IV	intravenous(ly)
IVSS	Intravenous Solution Stabilizer
LEN	Lenalidomide
mAb	monoclonal antibody
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NK	natural killer
NOS	not otherwise specified
OR	objective response
ORR	objective response rate
OS	overall survival
OUS	outside United States
PBML	primary mediastinal large B-cell
PD	progressive disease
PE	physical exam
PET/CT	combined positron emission tomography with computerized tomography
PFS	progression-free survival
PI	package insert
PK	pharmacokinetics
PO	by mouth
PR	partial response
PRR	partial response rate
PT	prothrombin time
Q2W	every 2 weeks
RBC	red blood cell
RDW	red blood cell distribution width
RP2D	recommended Phase 2 dose
R/R	relapsed or refractory
RTSM	randomization and trial supply management
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2 of the genus betacoronavirus
scFv	single-chain variable fragment (immunoglobulin fusion protein)

Abbreviations and Specialist Terms	Explanation
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBNK	T-, B-, and NK cells
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TTF	time to treatment failure
ULN	upper limit of normal
WBC	white blood cell
w/v	weight-to-volume

2. INTRODUCTION

2.1. Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma (NHL). Since the introduction of the anti-CD20 antibody rituximab, approximately 50% to 70% of patients may achieve cure with initial standard-of-care immunochemotherapy. For patients who are refractory to or relapse after frontline therapy, prognosis is poor. Salvage chemotherapy followed by high-dose chemotherapy and autologous stem-cell transplantation (ASCT) has some benefit in this setting and is associated with significant toxicities. Moreover, most patients are ineligible for this approach and have fewer treatment options. Recent therapeutic advances, such as chimeric antigen receptor T-cell therapy (CAR-T) and tafasitamab (US: Monjuvi®; EU: Minjuvi®) plus lenalidomide (Revlimid®), have potential to improve patient outcomes. Despite these advances, a significant need remains to provide effective treatment options for patients with relapsed or refractory (R/R) DLBCL who are ineligible for ASCT (Coiffier, 2016).

2.2. CD20 as a Therapeutic Target

The introduction of the anti-CD20 monoclonal antibody (mAb) rituximab for B-cell lymphoma in the late 1990s inaugurated a new era of cancer therapy (Maloney, 1994). In principle, mAbs are an amalgamation of 2 desirable characteristics of an anticancer drug, and rituximab exemplifies these qualities. First, rituximab is a therapy targeted to the tumor cell and carries fewer side effects than chemotherapy. Second, with its ability to directly stimulate the host immune system, it can potentially induce stronger, more long-lasting anti-tumor effects that bypass immunosuppressive factors. CD20 is an ideal target for monoclonal antibody therapy, since most B-cell neoplasms consistently express it, but normal B lineage stem cells and plasma cells do not allow B-cell repopulation and immunoglobulin production to continue, at least over several years (Stashenko, 1980). Rituximab (Rituxan®, Truxima®, MabThera®) and other similar therapeutic anti-CD20 mAbs such as iodine-131 tositumomab (Bexxar®), ofatumumab (Arzerra® and Kesimpta®), and obinutuzumab (Gazyva®) have been largely effective in realizing these aims, with impressive efficacy coupled with modest toxicity (Illidge, 2015; Robak, 2016).

However, there are limitations to these gains. Approximately 30% of cases of B-cell NHL either do not respond to rituximab or relapse after initially responding, and eventually become refractory to rituximab (Stolz, 2009). Also, rituximab has good activity against tumor masses and circulating tumor cells but has significantly less ability to clear tumor from bone marrow and lymph nodes (Mraz, 2011). Clearly, the ability of rituximab to strongly activate immune killing of tumor cells needs to be improved, especially in certain compartments of the body, while maintaining its tolerable side-effect profile.

Resistance to anti-CD20 monoclonal antibody therapy also remains a problem, although the mechanism of this resistance is still somewhat unclear. Recently, new anti-CD20s have entered the clinic to address this issue. Ofatumumab (type I) and obinutuzumab (type II) were both approved by the United States Food and Drug Administration (FDA) in 2009 and 2013,

respectively, for the treatment of chronic lymphocytic leukemia (CLL; Lee [B], 2014; Lemery, 2010). These antibodies have characteristics that theoretically should improve their efficacy over rituximab (Alduaij, 2011; Niederfellner, 2011; Rafiq, 2013; and Teeling, 2004). The hope is that the new anti-CD20 mAbs will be more efficacious than rituximab, but the clinical data so far are mixed. One study of a head-to-head comparison between rituximab and obinutuzumab in relapsed indolent lymphoma showed no difference in progression-free survival (PFS; Sehn, 2007). In a head-to-head comparison in patients with CLL (Goede, 2014), obinutuzumab was superior to rituximab when combined with chlorambucil, but the doses and schedules of the 2 mAbs were not matched. In short, although in vitro and xenograft studies support the potential of the new anti-CD20 mAbs over rituximab, the available clinical data are unclear as to whether these new mAbs are indeed an advance.

2.3. Treatment Descriptions

2.3.1. Plamotamab (XmAb13676) Product Description

Plamotamab (XmAb13676) is a humanized bispecific antibody (bsAb) that binds both CD3 and the tumor antigen CD20 in order to recruit cytotoxic T cells to kill CD20 tumor cells. Plamotamab has been designed to maintain full-length humanized monospecific antibody properties in a bsAb, enabling the design of stable molecules with favorable in vivo half-life, and allowing for the use of standard antibody production methods.

Antibody discovery programs at Xencor have demonstrated that several bsAbs based on this format are highly but selectively active towards target cells in primate models. See Section 2.4 for human experience with plamotamab.

2.3.2. Tafasitamab Product Description

Tafasitamab (tafasitamab-cxix) is a CD19-directed cytolytic antibody indicated for use in the US in combination with lenalidomide for the treatment of adult patients with R/R DLBCL not otherwise specified (NOS), including DLBCL arising from low-grade lymphoma, and who are not eligible for ASCT. Tafasitamab is also approved in the EU and is indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with relapsed or refractory DLBCL who are not eligible for ASCT. Tafasitamab is a humanized CD19-directed cytolytic monoclonal antibody that contains an IgG1/2 hybrid Fc-domain with 2 amino acid substitutions to modify the Fc-mediated functions of the antibody. It is produced by recombinant DNA technology in mammalian cells (Chinese hamster ovary). Tafasitamab has a molecular weight of approximately 150 kDa (see US Monjuvi® PI, 2021; EU Minjuvi® SmPC, 2021).

2.3.3. Lenalidomide Product Description

Lenalidomide, a thalidomide analogue, is an immunomodulatory agent (IMiD®) with antiangiogenic and antineoplastic properties. It is indicated for the treatment of adult patients with multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma, follicular lymphoma, and marginal zone lymphoma. See Revlimid® PI, 2021 or Revlimid® SmPC, 2022 for more information.

2.4. Human Experience with Plamotamab

Plamotamab is being studied in a Phase 1 study, XmAb13676-01 (A Phase 1 Multidose Study to Evaluate the Safety and Tolerability of XmAb®13676 in Patients with CD20-Expressing Hematologic Malignancies). As of 18 August 2021, a total of 96 subjects have been treated with plamotamab in the XmAb13676 01 study at weight-based dose levels of 0.7 to 360 µg/kg and flat dose levels of 0.8 to 50 mg. Of those 96 subjects, 80 were in the NHL group and 16 were in the CLL group. Adverse events (AEs) have been reported in 100% of the 80 NHL subjects. The most frequent AEs (>20%) in the NHL group were cytokine release syndrome (51/80, 63.8%), pyrexia (43/80, 53.8%), anemia (34/80, 42.5%), fatigue (24/80, 30.0%), nausea (21/80, 26.3%), diarrhea and cough (20/80, 25.0%), constipation (19/80, 23.8%), chills, headache, hypokalemia, and thrombocytopenia, (18/80, 22.5%), asthenia, dizziness, dyspnoea, hypotension, and neutropenia (17/80, 21.3%). Cytokine release syndrome (CRS), a predicted toxicity for this class of drugs, has occurred in subjects treated at 7.5, 10, 20, 25, 45, 50, 80, 125, 170, 250 µg/kg and at 0.8, 2, 20, 35 mg; however, CRS has not yet been seen at the highest dose levels of 360 µg/kg and 50 mg, in this study. The pattern of these events has differed in the NHL versus the CLL cohorts in this study.

2.4.1. Non-Hodgkin's Lymphoma: Escalation Cohorts

In the NHL escalation cohorts, the events have been predominantly Grade 1 or 2 in severity, with the exception of 4 out of 80 (5.0%) subjects who each experienced ≥ Grade 3 CRS, assessed according to American Society for Transplantation and Cellular Therapy (ASTCT) 2019 criteria, all associated with the first infusion of plamotamab. Manifestations of CRS have included fever, hypotension, tachycardia, chills, rigors, hypertension, headache, hypoxia, and elevations of liver enzymes. During the XmAb13676-01 study, cases of transaminase elevation, with or without bilirubin elevation, have occurred in the setting of CRS. The events were transient and reversible, with the transaminase and bilirubin levels returning to normal usually within 5 days. Five subjects (5/80, 6.3%) in the NHL cohort died during the study due to AEs, 3 due to COVID-19 (3/80, 3.8%), one of respiratory failure (1/80, 1.3%), and one due to unknown reasons (1/80, 1.3%).

2.4.2. Non-Hodgkin's Lymphoma: Flat-Dosing Cohorts

In the flat-dosing cohort (Cohort 1N-C, weekly titration of 0.8, 2, 20, 35 and 50 mg, followed by weekly dosing of 50 mg until Cycle 3 then every-two-week dosing of 50 mg) of NHL subjects, data are available for 14 subjects as of 18 August 2021. Of those subjects, the most frequent AEs (> 20%) were cytokine release syndrome (8/14, 57.1%), nausea (7/14, 50.0%), pyrexia and anemia (6/14, 42.9%), asthenia (4/14, 28.6%), fatigue, diarrhea, headache, dizziness, dyspnoea, hypotension, decreased appetite, alanine aminotransferase (ALT), increased back pain, peripheral

oedema, and aspartate aminotransferase (AST) increased (3/14, 21.4%). All CRS events, assessed according to ASTCT 2019 criteria, were Grade 1 or 2. In this cohort, manifestations of CRS occurring in more than 1 subject included pyrexia (7/8, 87.5%), hypotension (5/8, 62.5%), hypoxia and tachycardia (3/8, 37.5%), and headache (2/8, 25.0%). Anemia and lymphopenia were the only Grade 3 or 4 events reported in more than 1 subject (2/14, 14.3%). A single subject (1/14, 7.1%) died of COVID infection in this cohort.

Efficacy in the NHL population as measured by overall response rate (objective response rate [ORR], complete response [CR] plus partial response [PR]) and was observed in nearly all cohorts, with responses seen more consistently in cohorts with a top dose of greater than 80 µg/kg. Table 2 below presents the responses by cohort, as of 18 August 2021, for cohorts with a top dose of greater than or equal to 80 µg/kg in the efficacy evaluable population for NHL. The proposed plamotamab flat dosing regimen for the XmAb13676-03 study is represented below as “50 mg.”

Table 2: Overall Response Rate, Complete Response and Disease Control Rate for Overall Population and by Top Dose Level in Subjects with NHL from Study XmAb13676-01

Top Dose/Response	Efficacy Evaluable Population
Overall	
ORR	24/55 (43.6)
CR	11/55 (20.0)
DCR	32/55 (58.2)
80 µg/kg	
ORR	1/5 (20.0)
CR	0/5
DCR	2/5 (40.0)
125 µg/kg	
ORR	6/16 (37.5)
CR	5/16 (31.3)
DCR	10/16 (62.5)
170 µg/kg	
ORR	4/8 (50.0)
CR	2/8 (25.0)
DCR	5/8 (62.5)
250 µg/kg[a]	
ORR	6/12 (50.0)
CR	1/12(8.3)
DCR	5/12 (41.7)
360 µg/kg	
ORR	2/5 (40.0)
CR	1/5 (20.0)
DCR	4/5 (80.0)
50 mg	
ORR	5/9 (55.6)
CR	2/9 (22.2)
DCR	5/9 (55.6)

CR = complete response; DCR = disease control rate; ORR = objective response rate.
[a] One subject received a single priming dose of 25 µg/kg and achieved a PR.
Note: Efficacy population is defined as Subjects who did not withdraw prior to 2 cycles and completed at least 75% doses (6 out of 8 doses) and have post-baseline response assessment data available; or subjects who withdrew due to AEs/death; or subjects who withdrew other than AEs/death and have completed at least 75% doses of the first cycle (3 doses out of 4).

DCR includes Complete Metabolic Response, Complete Response, Partial Metabolic Response, Partial Response, No Metabolic Response, and Stable Disease.

2.4.3. Recommended Phase 2 Dose

The Phase 1 study, XmAb13676-01 demonstrated that plamotamab is well tolerated up to the highest dose level tested and has activity in R/R DLBCL. Notably, the flat dosing Cohort 1N-C (weekly titration of 0.8, 2, 20, 35, and 50 mg, followed by weekly dosing of 50 mg until Cycle 3 then every-two-week dosing of 50 mg) had an acceptable rate of CRS, with no Grade 3 or 4 CRS and no CRS events after start of every 2-week dosing. Among the subjects in the 1N-C cohort, Grade 3 and 4 toxicities were limited to anemia, liver enzyme increases, and cytopenias, all at rates of less than 20%. No dose-limiting toxicities were observed among the 14 treated subjects.

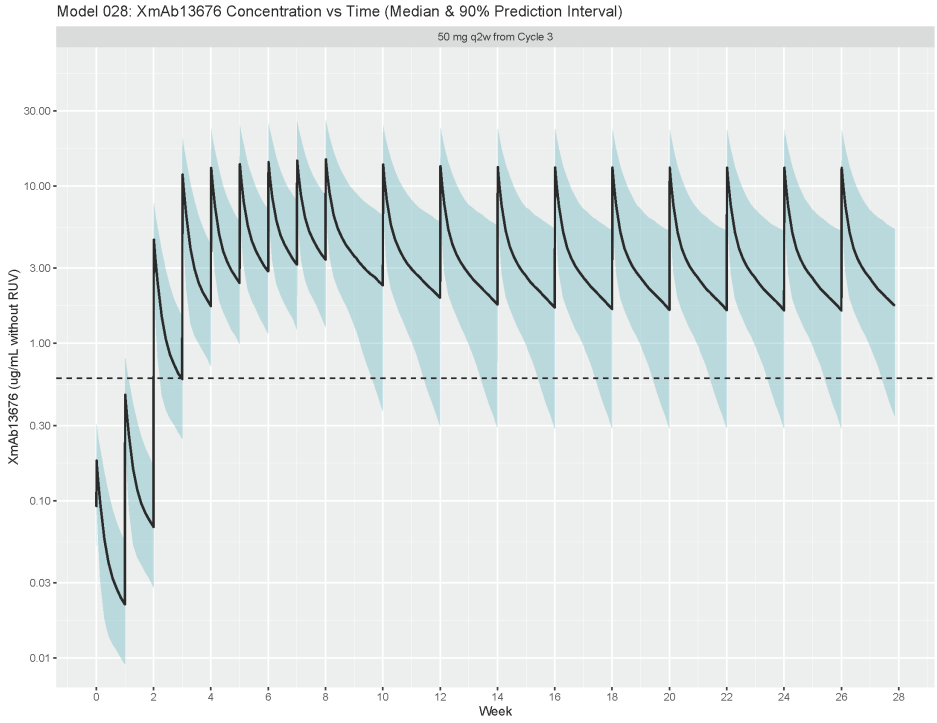
Preliminary exposure-response analysis based on the plamotamab pharmacokinetics (PK) and corresponding responses (ORR, CRS, others) in study XmAb13676-01 indicate a target trough concentration (C_{trough}) threshold of approximately 350 ng/mL (95% CI) to minimize the risk of CRS and a target C_{trough} threshold of approximately 650 ng/mL (95% CI) to maximize the probability of objective response. A population PK model was developed for plamotamab using interim data (April 2020) from the Phase 1 Study XmAb13676-01 that included plamotamab concentrations, actual sampling times, dosing histories, and baseline body weights from 53 subjects with NHL. Based on this model, the proposed dosing schemes in Part A of this study (XmAb13676-03) were simulated (predictions for high dose group shown in Figure 1). Population PK based predictions indicate that at the 20 mg dose, 77% of subjects exceed the safety threshold of 350 ng/mL, but only 52% of the subjects exceed the efficacy threshold of 650 ng/mL. At the 50 mg dose, 93% of subjects exceed the safety threshold of 350 ng/mL and 83% of the subjects exceed the efficacy threshold of 650 ng/mL. Based on these results, 50 mg dose group is more likely to provide a robust response across the population, but there exists significant variability in the estimate for target thresholds, and therefore further characterization of exposure response is desired at a range of concentrations in this study. Accordingly, this study evaluates two dose levels of plamotamab 20 mg and 50 mg at steady state that have been demonstrated to be well tolerated and active in the Phase 1 study.

This study includes a safety run-in that evaluates 2 dose levels of plamotamab with the standard doses of tafasitamab and lenalidomide. In addition to the recommended Phase 2 dose (RP2D), the study begins with a regimen that titrates to 20 mg: weekly titration of 0.8, 2, and 20 mg, followed by weekly dosing of 20 mg until Cycle 3 then every-2-week dosing of 20 mg. The titration from low minimally active dose to pharmacologically active doses was chosen to mitigate the risk of CRS based on clinical experience with plamotamab and other CD3-directed antibodies (Hosseini, 2020; Hutchings, 2021).

Tafasitamab is an Fc-modified monoclonal antibody that binds to CD19 antigen expressed on the surface of pre-B and mature B lymphocytes and on several B-cell malignancies, including DLBCL. Upon binding to CD19, tafasitamab-cxix mediates B-cell lysis through apoptosis and immune effector mechanisms, including antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis. In a Phase 1 clinical trial (Woyach, 2014), tafasitamab given at 12 mg/kg every 4 days reduced peripheral blood B cell counts by 97% after 8 days of treatment in patients

with relapsed or refractory DLBCL. Given that tafasitamab may promote B cell depletion, which could mitigate CRS with the addition of plamotamab + lenalidomide to the regimen, an 8-day, 2-dose run-in of tafasitamab at 12 mg/kg is included before C1D1. Other than the 2-dose tafasitamab monotherapy run-in, tafasitamab and lenalidomide will be administered according to the package inserts (PIs) or Summary of Product Characteristics (SmPCs; Monjuvi® PI, 2021; Minjuvi® SmPC, 2021; and Revlimid® PI, 2021; Revlimid® SmPC, 2022).

Figure 1: Log Scale Simulated Median Concentrations and 90% Prediction Intervals for Flat Dose and Schedule.



For doses beyond Week 12, the blue area above the line at 0.6 µg/mL illustrates the prediction that 85% of subjects maintain Q2W steady state troughs above the 0.6 µg/mL trough chosen to preserve benefit.

2.4.4. Benefit/Risk Assessment

It is anticipated that the addition of plamotamab to the combination of tafasitamab and lenalidomide will enhance efficacy, through higher response rates and longer time to progression due to the engagement of both CD19 and CD20 antigens with nonoverlapping mechanisms of resistance.

Plamotamab monotherapy demonstrated responses across nearly all dose levels above 80 µg/kg maximum dose, see Table 2. Within the NHL Efficacy Population, responses were observed in 24/55 (43.6%) with 11/55 subjects (20%) subjects achieving a CR. Further, responses were observed in 5/9 (55.6%) subjects in the NHL Efficacy Population treated at the RP2D. Tafasitamab and lenalidomide established efficacy in R/R DLBCL in a recent Phase 2 study with a response rate of 57.5% with 40% achieving a CR. PFS was 11.6 months (Duell, 2021). Regulatory approvals have been granted in the US and EU.

Although the RP2D of plamotamab monotherapy has been identified, the appropriate dose in combination with tafasitamab and lenalidomide has not been established. To assess the safety of plamotamab when it is used in combination with tafasitamab and lenalidomide, a safety run-in phase is planned in this study. The safety run-in phase will enroll subjects starting at a lower dose of plamotamab (see Table 3) prior to enrolling subjects at the RP2D. Safety will be assessed before proceeding to the randomized part of the study.

Other safety measures have been implemented. The step-up dosing regimen used in this study reduced CRS events to Grade ≤ 2 in the Phase 1 trial. In addition, the study requires the separation of the dosing of tafasitamab, plamotamab, and lenalidomide as well as including dose modifications of each product for specific toxicities, along with management guidelines for those toxicities.

These safety measures along with the efficacy observed with both plamotamab and tafasitamab in combination with lenalidomide, present a favorable benefit-risk ratio for subjects enrolling in this study.

3. TRIAL OBJECTIVES AND PURPOSE

3.1. Primary Objectives

To determine the safety and efficacy of the combination of plamotamab, tafasitamab, and lenalidomide compared to tafasitamab and lenalidomide in adult subjects with R/R DLBCL.

3.2. Secondary Objectives

The secondary objectives of the study are to compare a combination of plamotamab, tafasitamab, and lenalidomide to tafasitamab and lenalidomide as follows:

1. To compare rates of objective response (ORR = CRR + partial response rate [PRR]) by Blinded Independent Review Committee (BIRC) and Investigator per Lugano 2014 criteria

2. To compare overall survival (OS)

3. To compare time to treatment failure (TTF)

4. To assess duration of response (DOR) among subjects achieving an objective response (CR + PR) and among subjects achieving a CR by BIRC

5. To compare the PFS, as determined by the Investigator

6. To assess the incidence, timing, and severity of CRS by following CRS-related AEs including incidence and grade of AEs and incidence of serious adverse events (SAEs)

7. To assess the incidence, timing, and severity of neurological AEs and incidence and grade of immune effector cell-associated neurotoxicity syndrome

8. To assess the dose intensity of tafasitamab and lenalidomide in Part 1 when given in combination with plamotamab

9. To assess the safety profile of a combination of plamotamab, tafasitamab, and lenalidomide in Part 2 as determined by the incidence and severity of treatment-emergent adverse events (TEAEs), in adult subjects with R/R DLBCL

3.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

1. To assess the PK of plamotamab and tafasitamab

2. To assess the potential immunogenicity of plamotamab and tafasitamab

3. To explore the association of baseline CD19 and CD20 levels, molecularly defined DLBCL subtypes, minimal residual disease (MRD) as measured by circulating tumor DNA (ctDNA), and immune cell frequency, activation status, and function with clinical outcomes

4. To evaluate biomarkers of CRS (including but not limited to serum cytokine levels) with clinical outcomes

5. To assess potential associations between clinical outcomes and biologically and clinically defined subgroups, including but not limited to randomization strata and time since last rituximab treatment

3.4. Purpose of Study

The combination of tafasitamab in combination with lenalidomide has been granted accelerated approval in the US for use in patients with R/R DLBCL, NOS. Tafasitamab is an Fc-modified monoclonal antibody that binds to CD19 antigen expressed on the surface of pre-B and mature B lymphocytes and on several B-cell malignancies, including DLBCL. In combination with lenalidomide in a single-arm clinical trial (NCT02399085), tafasitamab had a 57.5% response rate in R/R DLBCL with a median DOR of 43.9 months and median PFS of 11.6 months (Duell, 2021). Plamotamab is a humanized bsAb that binds both CD3 and the tumor antigen CD20 in order to recruit cytotoxic T cells to kill CD20 tumor cells. In an ongoing Phase 1 study (Study XmAb13676-01, NCT02924402), plamotamab has produced durable responses in subjects with R/R DLBCL.

It is hypothesized that the engagement of both CD19 and CD20 antigens will enhance efficacy outcomes in this population, due to nonoverlapping mechanisms of resistance. Further, this combination activates and expands the innate immune system and adaptive effector cells as well as modulates the tumor microenvironment. These characteristics support and warrant a study of the combination of plamotamab, tafasitamab, and lenalidomide. The trial first determines if the combination of the 3 products can be safely administered and to determine the dose for Part 2. The second part of this trial is designed to determine the improvement in efficacy, as measured by PFS,

of the standard of care for DLBCL, tafasitamab and lenalidomide, with the addition of plamotamab to tafasitamab and lenalidomide.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a randomized, multicenter, open-label, Phase 2 study of plamotamab combined with tafasitamab plus lenalidomide versus tafasitamab plus lenalidomide in adult subjects with DLBCL who have relapsed after or are refractory to at least 1 prior line of therapy, which must have included multi-agent chemoimmunotherapy inclusive of an anti-CD20 monoclonal antibody, and who are not candidates for ASCT, refuse ASCT, or relapse after ASCT.

A central pathologist reading will confirm the diagnosis of DLBCL retrospectively after enrollment, using archival or recently obtained tissue. Central radiology and clinical reviewers will assess objective disease response according to the Lugano 2014 (Cheson, 2014) guidelines. Details of the central review will be provided in an imaging charter outlining functions and processes. In addition, Investigator-assessed response will be captured in the clinical database, and concordance analyses will be performed. All subjects will be treated until progression or withdrawal for other reasons and then followed for OS up to 5 years.

This study will consist of 2 parts which will be performed sequentially, with Part 1 enrolling and evaluating subjects for safety and determination of dose and schedule before the start of Part 2.

4.1.1. Part 1: Single-Arm, Safety Run-In

Part 1 consists of a single-arm evaluation of the safety of the triple combination of plamotamab combined with tafasitamab plus lenalidomide in at least 40 subjects in 2 cohorts of a minimum of 20 subjects per cohort:

- Cohort 1A treats subjects with the triple combination at plamotamab dose level –1 (Table 3).
- Cohort 1B commences enrollment after the Cohort 1A completes enrollment. Cohort 1B treats subjects with the triple combination at plamotamab dose level 1 (Table 3).
- An initial safety evaluation is conducted after all subjects in Cohorts 1A and 1B either receive treatment, at a minimum, through C4D28 or are discontinued prior to C4D28 due to an AE or progressive disease.

After the initial safety evaluation of both Cohorts 1A and 1B, the pharmacologically optimal dose of plamotamab (dose level -1 or dose level 1) with an acceptable safety profile will be advanced to the randomized (Part 2) portion of the study.

Table 3: Cohort 1A and Cohort 1B Plamotamab Dosing Regimen

Cohort	Dose Level	Cycle 1 Day 1 (Priming Dose)	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22	Cycle 2 Day 1	Cycle 2 Days 1, 8, 15, and 22	Cycle 3 and Subsequent Q2W Dosing
1A	-1	0.8 mg	2 mg	20 mg	20 mg	20 mg	20 mg	20 mg
1B	1	0.8 mg	2 mg	20 mg	35 mg	50 mg	50 mg	50 mg

Q2W = every 2 weeks.

4.1.2. Part 2: Open-Label Randomized

The open-label, randomized portion (Part 2) of the study will begin after an initial safety evaluation of at least 40 subjects from Part 1. Prior to the initiation of Part 2, the protocol will be revised with the dosing regimen selected from Part 1 and will include adequate justification to support the proposed dose/schedule in Part 2.

During Part 2, subjects are randomized in a 1:1 ratio to the 2 treatment arms, stratified by international prognostic index (IPI) risk score at baseline (Sehn, 2007; 3 to 5 versus 0 to 2), number of lines of prior therapy (1 versus ≥ 2), and primary refractory (yes versus no). Primary refractory enrollment is limited to 36 of 200 subjects. Part 2 will enroll approximately 200 subjects. The sample size for Part 2 may be adjusted based on the results from Part 1. An increase in the enrollment number beyond 200 will be made by a protocol amendment prior to the initiation of the randomized portion. An independent data monitoring committee (IDMC) will review safety data during Part 2 with meetings scheduled after 50, 100, and 150 subjects have been randomized. The primary analysis for PFS will occur after 89 disease progression and death events. An interim analysis for OS will be performed at that time (see Section 11.3).

4.2. Endpoints

4.2.1. Primary Endpoints

The primary endpoint of the study is

- For Part 1, safety as measured by incidence of CRS and TEAEs; and
- For Part 2, PFS, defined as the time from randomization to first documentation of progressive disease or death, whichever comes first, as assessed by the BIRC using Lugano 2014 criteria.

4.2.2. Secondary Endpoints

The secondary endpoints of the study are as follows:

1. Best ORR and CRR, as assessed by Investigator and by the BIRC according to Lugano 2014 criteria (Cheson, 2014)

2. OS, defined as the time from randomization to death from any cause

3. TTF, defined as the time from randomization to discontinuation of all study treatment for any reason, including disease progression (as assessed by Investigator and by BIRC), treatment toxicity, and death, whichever comes first

4. DOR, defined as the time from first response to progression or death due to any cause, whichever comes first, among subjects achieving an objective response (OR) and among subjects with CR as assessed by BIRC

5. PFS, as assessed by Investigator using Lugano 2014 criteria

6. Incidence, timing, and severity of CRS as assessed by following CRS-related AEs, including incidence and grade of AEs and incidence of SAEs, with CRS grading defined by the ASTCT Consensus Grading

7. Incidence, timing, and severity of neurological AEs, and incidence and grade of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

8. Dose intensity of tafasitamab and lenalidomide as measured by planned and actual dose administration in Part 1

9. Incidence and severity of TEAEs in Part 2, with severity defined by the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

4.2.3. Exploratory Endpoints

The exploratory endpoints of the study are as follows:

1. PK concentrations of plamotamab and tafasitamab

2. Anti-plamotamab and anti-tafasitamab antibodies

3. Absolute counts and percentage change from baseline in measurements of B-, T-, and natural killer (NK) cell populations

4. Analyses of exploratory and diagnostic biomarkers (including, but not limited to, cell of origin by Hans algorithm [germinal center B-cell (GCB) versus non-GCB], CD10, CD19, CD20, MUM1, BCL2, and BCL6 expression); peripheral and intratumoral leukocyte frequencies, phenotyping, functional and activation markers at baseline and on treatment; gene expression profiling for cell of origin subtyping and exploratory transcriptomic analysis, and genomic analysis in tumor including, but not limited to, FcR genotyping and MRD ctDNA analysis in blood

5. Rituximab concentrations at baseline

6. Biomarkers of CRS; eg, serum cytokine levels

7. Randomization strata and baseline characteristics subgroup analyses of ORR, PFS, OS and TTF

4.3. Treatment Regimens

This study consists of 2 parts:

- Part 1: single-arm, two-cohort, safety run-in
- Part 2: open-label, randomized, two-arm efficacy and safety

4.3.1. Part 1: Single-Arm, Safety Run-In

Part 1 is a single-arm, two-cohort, safety run-in intended to establish the safety of the combination of plamotamab, tafasitamab, and lenalidomide.

Treatment consists of the combination of plamotamab, tafasitamab, and lenalidomide administered in 28-day cycles, with 2 priming doses of tafasitamab before Cycle 1. Plamotamab and tafasitamab can be administered until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first; however, lenalidomide can be given for only up to a total of 12 cycles. Tafasitamab and plamotamab must not be administered simultaneously. On days when both tafasitamab and plamotamab are given, the tafasitamab should be given first followed by plamotamab. It is recommended that the infusions are separated by at least 2 hours.

4.3.2. Part 2: Open-Label, Randomized

Part 2 is an efficacy cohort where subjects are randomized to receive Arm A or Arm B as follows:

Arm A:

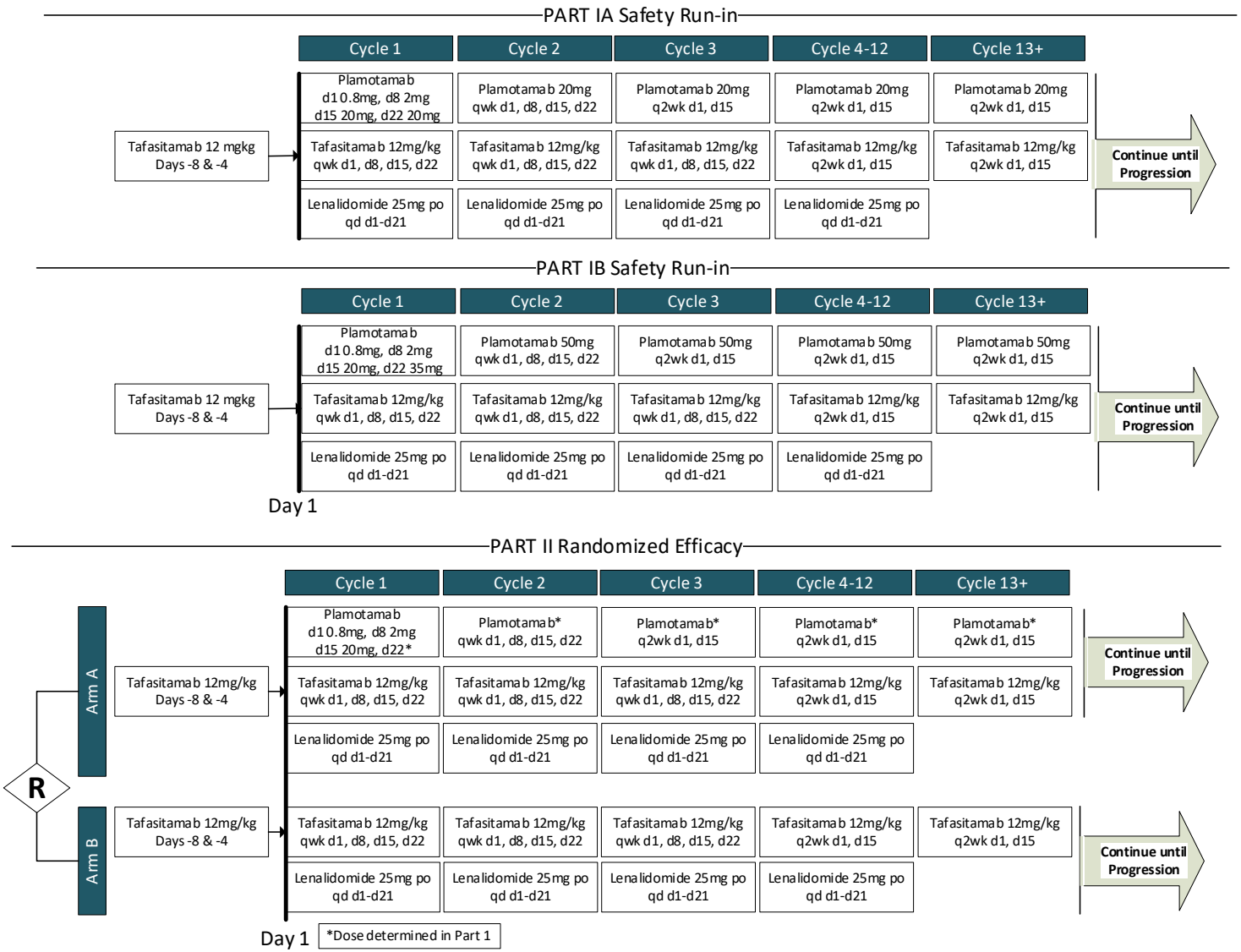
Treatment consists of the combination of plamotamab, tafasitamab, and lenalidomide administered in 28-day cycles, with 2 priming doses of tafasitamab before Cycle 1. Plamotamab and tafasitamab can be administered until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first. Lenalidomide can be given for up to a total of 12 cycles.

Arm B:

Treatment consists of the combination of tafasitamab and lenalidomide administered in 28-day cycles with 2 priming doses of tafasitamab before Cycle 1. Tafasitamab can be administered until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first. Lenalidomide can be given for up to a total of 12 cycles.

Part 1 and Part 2 dose and schedule are presented in the schematic below (Figure 2):

Figure 2: Dosing Schema



4.4. Number of Subjects

Part 1 will enroll at least 40 subjects into 2 cohorts with a minimum of 20 subjects per cohort.

Part 2 will enroll approximately 200 subjects. The sample size for Part 2 may be adjusted based on the results from Part 1. Any increase in the enrollment number beyond 200 will be made by a protocol amendment prior to the initiation of the randomized portion. Primary refractory enrollment will be limited in Part 2 to 36 of 200 subjects.

Overall, the study is planned to enroll approximately 240 subjects.

4.5. Treatment Assignment

Treatment assignment for Part 1 and randomization for Part 2 will be performed via a third-party randomization and trial supply management (RTSM)/interactive response technology (IRT) system.

4.5.1. Part 1: Single-Arm Safety Run-In

During the Part 1 safety run-in, 40 subjects will be enrolled and treated with plamotamab and tafasitamab plus lenalidomide (ie, single-arm, uncontrolled). The subjects will be considered enrolled if they have signed the informed consent, are determined to be eligible, and receive the Day –8 tafasitamab priming dose.

4.5.2. Part 2: Open-Label Randomized

During Part 2, a total of 200 subjects will be randomized as follows: with a 1:1 ratio of plamotamab and tafasitamab plus lenalidomide versus tafasitamab plus lenalidomide, stratified by IPI risk score at baseline (3 – 5 versus 0 – 2); number of lines of prior therapy (1 versus ≥ 2); and primary refractory (yes versus no). A maximum of 36 primary refractory subjects may be enrolled. Subjects will be randomized only if they have signed the informed consent and are determined to be eligible. The initiation of study treatment will occur within 72 hours of randomization. Study treatment will begin on Study Day –8 with the tafasitamab priming doses.

No blinding is specified given the potential for overlapping toxicities. In the presence of overlapping toxicities, a blinded study may result in dose modifications or reductions of placebo. This may confound the management of toxicities without addressing the source of the toxicity through dose modification or reduction schemes. Therefore, to ensure the safety of subjects, the study will not be blinded.

4.5.3. Subject Screening and Enrollment Numbers

Subjects who consent for the study will be assigned a **Subject Screening Number**, a site sequential 8-digit number. The first 3 numbers designate the site number then hyphen, then 5 more numbers for the subject number beginning with 9 for screening (ie, 101–90001).

Subjects who will be eligible to receive study treatment (Part 1) or be randomized (Part 2) will be assigned a **Subject Enrollment Number**, a study sequential 8-digit number, first 3 numbers for the site number, then hyphen, and then 5 more numbers for the subject number (ie, 101–10001).

4.6. Management of Toxicities

The combination of plamotamab, tafasitamab and lenalidomide has not yet been tested in humans. Safety data are available for plamotamab and for the combination of tafasitamab and lenalidomide. Important and potentially overlapping toxicities have been identified and are outlined below. However, new toxicities of the 3-drug regimen may be identified during this study, and investigators should be diligent in the monitoring and management of subjects during treatment. Management of known toxicities such as CRS, infusion-related reactions, hematologic toxicities, and tumor lysis syndrome are outlined by treatment regimen in the following sections.

4.6.1. Cytokine Release Syndrome

The ASTCT defines CRS as "a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end organ dysfunction" (Lee, 2019).

CRS can present with a variety of symptoms ranging from mild, flu-like symptoms to severe life-threatening manifestations of the inflammatory response. Mild symptoms of CRS include fever, fatigue, headache, rash, arthralgia, and myalgia. More severe cases are characterized by hypotension as well as high fever and can progress to an uncontrolled systemic inflammatory response with vasopressor-requiring circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure (Shimabukuro-Vornhagen, 2018). CRS is more likely to occur after the first dose of plamotamab than subsequent doses, tends to begin somewhat later than hypersensitivity reactions, and is more likely to be associated with hepatic and neurologic complications. Plamotamab associated CRS Symptoms observed in the Phase 1 study include:

- Aphasia or word-finding difficulty
- Arthralgia
- Confusion/mental status changes/delirium
- Serum creatinine increase
- Diaphoresis
- Dizziness
- Dyspnea
- Fatigue (asthenia, lethargy, malaise)
- Fever
- Gait disturbance/dysmetria
- Headache
- Hypotension/hypertension
- Hypoxia
- Myalgia
- Nausea/vomiting
- Rigors/chills
- Tachycardia
- Tachypnea
- Seizures
- Transaminitis/hyperbilirubinemia
- Tremor

CRS toxicity is defined using the ASTCT CRS Consensus Grading (Lee, 2019). See Table 4 for these definitions.

Table 4: American Society for Transplantation and Cellular Therapy Cytokine Release Syndrome Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
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[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.
Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading.

[a] Fever is defined as temperature ≥ 38 °C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven 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 subject with temperature of 39.5 °C, hypotension requiring 1 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/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

Source: Lee, 2019.

4.6.1.1. Safety Run-in and Part 2, Arm A (Plamotamab, Tafasitamab and Lenalidomide)

Plamotamab is known to cause CRS. CRS has not been observed in clinical trials of tafasitamab and lenalidomide. However, lenalidomide, through its potential to activate T cells, may potentiate CRS in combination with plamotamab. In addition, to avoid the overlap of CRS caused by plamotamab with tafasitamab-induced, infusion-related reactions, plamotamab must always be given after tafasitamab if administered on the same day. See Section 4.7 for dose modification of lenalidomide and plamotamab in the instance of CRS.

4.6.1.2. Part 2, Arm B (Tafasitamab and Lenalidomide)

CRS has not been observed in clinical trials of tafasitamab and lenalidomide. If CRS is observed with tafasitamab, follow treatment guidelines provided for plamotamab and contact the medical monitor as soon as possible.

4.6.1.3. Cytokine Release Syndrome Versus Allergic/ Hypersensitivity/ Infusion-related Reactions

CRS is mechanistically different from allergic/hypersensitive/Infusion-related reactions (Brennan, 2010), although some of the manifestations are common to both AEs and both have been reported to occur with therapeutic antibodies. It is less clear how cytokine release is triggered, although it is likely to be associated with immune cell activation; in this case, CD3-expressing lymphocytes may be the prime effector of CRS. See Section 4.6.2 for management of allergic/hypersensitive/infusion-related reactions.

4.6.1.4. Management of Cytokine Release Syndrome

Management of CRS should be per standard investigational site procedures. Alternatively, if there are no local standards or if they are incomplete, the approaches discussed below may be used.

Contact the Xencor Medical Monitor immediately if questions arise concerning the management of an infusion reaction/CRS/neurotoxicity.

Medical Monitor's contact information:

[redacted]
Telephone: [redacted]
E-mail: [redacted]

4.6.1.4.1. Use of Tocilizumab for Cytokine Release Syndrome

Tocilizumab (Acterma®) is a therapeutic antibody that interferes with the binding of interleukin-6 (IL-6) to the IL-6 receptor. It has been used to decrease the severity and, possibly, the mortality of severe CRS (Frey, 2017), and early administration may be useful in improving outcomes. Suggested guidelines for its use are in Section 4.6.1.6, in addition:

- Have sufficient tocilizumab (dose of 8 mg/kg) readily available to the area where subjects are receiving their infusions and being observed post-infusion.
- Repeat dosing of tocilizumab may be necessary if signs and symptoms persist or return after initial treatment

Tocilizumab is the preferred IL-6 antagonist, however, if tocilizumab is unavailable either regionally or due to limited supply, follow institutional or local guidelines for the treatment of CRS until tocilizumab is available.

4.6.1.5. Fluid Management

CRS is sometimes associated with myocardial dysfunction, pulmonary edema, or capillary leak syndrome (Shimabukuro-Vornhagen, 2018). Although there are little or no data regarding use of anti-CD3 antibodies and the need for fluid management, it seems prudent to monitor subjects for weight gain and limit intravenous (IV) fluid administration in the acute setting. Following are guidelines for managing fluids:

- If a subject is noted to have had a ≥ 10% increase in body weight over the previous 2 weeks in association with new or significantly increased bilateral lower extremity edema, delay dosing until this finding is evaluated and, if indicated, treated.

- For acute hypotension, limit an IV fluid bolus to 500 to 1000 mL of normal saline or the equivalent.

- If there is not an adequate response to fluids, consider treatment with tocilizumab (and vasopressors, if necessary) rather than additional fluid boluses.

4.6.1.6. Cytokine Release Syndrome Treatment Guidelines by ASTCT CRS Consensus Grade

The CRS treatment guidelines are listed below by grade:

Grade 1

- Symptomatic management is recommended. Administer acetaminophen 650 mg orally as an antipyretic or analgesic and/or diphenhydramine 25 to 50 mg intravenously or orally for rash, pruritus, or other signs and symptoms of hypersensitivity (allergic) reaction if clinically indicated.

- Measure vital signs every 15 minutes or less, as clinically indicated.

- Obtain an unscheduled blood sample for cytokine analysis during the event and approximately 4 hours later, unless scheduled cytokine monitoring is already in progress on the same visit day.

- Monitor the subject for worsening of condition; if severity of event increases to a higher grade, stop the infusion, administer steroids as above, and refer to guidelines below for more severe reactions.

Grade 2

- Hypotension responsive to fluids not requiring a vasopressor, or mild respiratory symptoms treatable with low-flow oxygen, are signs of Grade 2 toxicity. Older subjects or those with significant comorbidities may be at a higher risk of decompensation in this situation.

- Discontinue the infusion and consider administration of additional dexamethasone at a dose of 10 to 20 mg intravenously; acetaminophen 650 mg orally and/or diphenhydramine 25 to 50 mg intravenously or orally may also be given to treat signs and symptoms.

- Once symptoms have resolved, restart the infusion at 50% of the baseline rate. If after 1 hour, the subject's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to the baseline rate.

- Measure vital signs every 15 minutes or less as clinically indicated. For subjects who can tolerate an increase in the infusion rate back to baseline and maintain normal blood pressure for 30 minutes after the rate increase then, at the discretion of the Investigator, the frequency of vital sign assessment may be reduced to every 30 minutes during the infusion.

- Obtain an unscheduled blood sample for cytokine analysis during the event and approximately 4 hours later, unless scheduled cytokine monitoring is already in progress on the same visit day.

- Monitor the subject for worsening of condition; if severity of event increases to a higher grade, stop the infusion, administer appropriate treatment, and refer to guidelines below for Grades 3 and 4 reactions.

- Note that older subjects or those with significant comorbidities may be at higher risk of decompensation in this situation. When reactions occur in these vulnerable subjects, or in the case of rapidly progressing reactions, consider treatment with tocilizumab 8 mg/kg IV over 1 hour, with or without additional dexamethasone 10 to 20 mg IV (or equivalent).

Grade 3 and 4

- Stop the infusion and disconnect the infusion tubing from the subject.

- Administer additional dexamethasone 10 mg intravenously.

- Immediately give aggressive supportive care. Use pressors, fluids, oxygen, epinephrine or bronchodilators, ventilatory support, antipyretics, and analgesics as indicated.

- Treatment with tocilizumab, 8 mg/kg IV over 1 hour (Hallek, 2018), is encouraged for CRS due to the high risk of progression and permanent organ dysfunction.

- Hospital admission for observations is almost always indicated, usually to an intensive care unit, since an initial appearance of improvement may quickly yield to rapid decompensation.

- Subjects with Grade 3 CRS or infusion reaction may be rechallenged once resolved as described in Section 4.7 and Table 8. Subjects with recurrent Grade 3 or any Grade 4 reaction should not receive further plamotamab treatment but will continue to be followed on the protocol (ie, followed for long-term survival).

- Obtain an unscheduled blood sample for cytokine analysis during the event and approximately 4 hours later, unless scheduled cytokine monitoring is already in progress on the same visit day.

- Obtain an unscheduled sample for anti-drug antibodies (ADA) testing as close to the onset of the event as possible, at the resolution of the event, and approximately 28 days

following the event, unless scheduled cytokine monitoring is already in progress on the same visit day.

- Notify the Xencor Medical Monitor immediately.

4.6.1.7. Neurotoxicity

In addition to CRS, another toxicity observed after CAR-T cell therapy and CD3 bispecific antibodies is neurotoxicity. Immune effector cell-associated neurotoxicity syndrome (ICANS) may manifest as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and, rarely, cerebral edema (Lee, 2019). Neurotoxicity was previously considered in aggregate with CRS, but is now treated separately, due to its timing and response to treatment.

Neurologic symptoms may occur during or after CRS symptoms, but rarely precede CRS symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy. Headache is a nonspecific symptom, frequently occurring during fever or after chemotherapy in patients without other neurologic dysfunction. Thus, headache alone is not a useful marker of ICANS. Expressive aphasia, on the other hand, appears to be a very specific symptom of ICANS (Lee, 2019).

A consensus grading scheme, which is a slightly modified version of the CARTOX-10 screening tool, which incorporates key elements of the mini-mental state examination, the immune effector cell-associated encephalopathy (ICE) score, will be used for the grading of ICANS (Table 5). It is important to note that the 10-point ICE screening tool is helpful for assessing subjects for encephalopathy; however, the grading of ICANS requires assessment of the 10-point ICE score as well as evaluation of other neurologic domains, such as level of consciousness, motor symptoms, seizures, and signs of elevated intracranial pressure /cerebral edema, which may occur with or without encephalopathy. The ASTCT ICANS toxicity grading system is shown in Table 6. This grading scale will be used to assess neurotoxicity, rather than the CTCAE version 5.0.

Table 5: Immune Effector Cell-Associated Encephalopathy Scoring

ICE
Orientation: orientation to year, month, city, hospital: 4 points
Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points
Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
Attention: ability to count backwards from 100 by 10: 1 point

ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated. Encephalopathy (score).
Scoring: 10, no impairment;
7 – 9, Grade 1 ICANS;
3 – 6, Grade 2 ICANS;
0 – 2, Grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, Grade 4 ICANS (Lee, 2019).

Table 6: American Society for Transplantation and Cellular Therapy Immune Effector Cell-Associated Neurotoxicity Syndrome Consensus Toxicity Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7– 9	3 – 6	0 – 2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

EEG = electroencephalogram; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy (score); ICP = intracranial pressure; N/A = not applicable; VI = sixth.
ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

[a] A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4.

[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[c] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0 (Lee, 2019).

It has been speculated that high levels of IL-6 may directly mediate neurotoxicity in this situation (Lee [A], 2014). A human anti-IL-6 monoclonal antibody, tocilizumab, may reverse this

neurotoxicity, but it would not be expected to cross the blood brain barrier, and efficacy in this setting has not been confirmed. Therefore, it is suggested that corticosteroids be the primary therapy in this situation, and tocilizumab considered only if this proves ineffective.

Clinical management of neurotoxicity:

- Monitor subjects closely for signs and symptoms of these events (including the use of mental status and neurologic examinations).
- If neurotoxicity becomes evident, draw an unscheduled blood sample for cytokine analysis at that time, and again 4 hours later, unless scheduled cytokine monitoring is already in progress on the same visit day.
- If neurologic toxicity is Grade 4, discontinue plamotamab.
- For Grade 3 neurologic toxicity, withhold drug until the toxicity has recovered to ≤ Grade 1 (mild) and has remained at ≤ Grade 1 for at least 3 days before restarting therapy. Restart at 75% of the previous dose. Escalate back to full dose at the time of the next dose if ≥ Grade 2 toxicity does not recur. If ≥ Grade 2 toxicity reoccurs at 75% dose, or if < Grade 2 toxicity takes more than 7 days to resolve, discontinue permanently. If Grade 3 neurologic toxicity persists for more than 7 days, permanently discontinue plamotamab.
- For severe neurologic symptoms, administer additional dexamethasone 10 mg intravenously and repeat every 12 hours if symptoms do not abate rapidly.
- For recurrent seizures, anticonvulsant therapy may be necessary.

4.6.2. Allergic/Hypersensitivity/Infusion-related Reactions

Infusion-related reactions have been reported for tafasitamab as well as plamotamab. An allergic reaction is often caused by a type 1 hypersensitivity mechanism due to immunoglobulin E (IgE)-mediated release of histamines and prostaglandins, although a direct interaction with mast cells and basophils can also occur. However, infusion-related reactions, including serious and fatal reactions, are not uncommon with monoclonal antibody therapeutics and tend to occur most frequently during the first few infusions.

Signs and symptoms usually develop during or shortly after drug infusion in hypersensitivity reactions, are more likely to occur after several doses of the drug and are largely related to histamine release. Typical signs and symptoms include rash/urticaria, flushing, pruritus, fever, dyspnea, cough, and hypotension, although the following may also occur (Lenz, 2007):

- Arthralgia
- Bronchospasm
- Confusion/mental status changes/delirium
- Dizziness
- Fatigue (asthenia, lethargy, malaise)
- Hallucinations
- Headache

- Hypertension
- Myalgia
- Nausea/vomiting
- Rigors/chills
- Diaphoresis
- Tachycardia

Allergic/hypersensitivity/infusion-related reactions are managed according to institutional practices and guidelines. Allergic/hypersensitivity reactions will be defined according to the NCI-CTCAE, Version 5.0 (NCI-CTCAE, 2017) definition of allergic reaction.

4.6.2.1. Safety Run-in and Part 2, Arm A (Plamotamab, Tafasitamab and Lenalidomide)

Infusion-related reactions have been observed with plamotamab and tafasitamab. To mitigate overlapping toxicity with plamotamab, on a given treatment day, tafasitamab must be given first with a minimum of 2 hours between the end of the tafasitamab infusion and the start of the plamotamab infusion. If a > Grade 1 infusion reaction occurs with tafasitamab, delay the plamotamab until the resolution all symptoms of the reaction. Depending on the timing of the resolution of all symptoms, it may be necessary to administer the plamotamab the following day.

4.6.2.2. Part 2, Arm B (Tafasitamab and Lenalidomide)

Infusion-related reactions have been observed with tafasitamab and lenalidomide. Follow toxicity management instructions provided in the prescribing information for tafasitamab. Refer to Section 4.7 for dosage modifications.

4.6.3. Hematologic Toxicities

Hematologic toxicities, specifically decreases in absolute neutrophil count (ANC) and platelet count, have been observed in clinical trials of tafasitamab and lenalidomide. Decreases in platelets and ANC have also been observed with plamotamab (see Table 7).

Table 7: Adverse Events of Neutropenia and Thrombocytopenia with Tafasitamab/Lenalidomide and Plamotamab (All Grades)

	Tafasitamab[a]/Lenalidomide	Plamotamab[b]
Neutropenia	51%	20.8%
Thrombocytopenia	31%	24.0%

[a] Monjuvi® PI, 2021; Minjuvi® SmPC, 2021
[b] Plamotamab Investigator's Brochure, 2021

These decreases may worsen in grade or duration when the products are given in combination. Monitor blood counts carefully and follow institutional guidelines for the treatment of neutropenia and thrombocytopenia. Treatment may include the use of growth factors and the administration of whole blood/blood product transfusions. Management may also include the delay in the administration of study drugs until the counts return to at least Grade 2 levels. See Section 4.7 for any dose modifications to study drugs.

4.6.3.1. Safety Run-in and Part 2, Arm A (Plamotamab, Tafasitamab and Lenalidomide)

Hematologic toxicities, specifically, decreases in ANC and platelet counts have been observed in clinical trials of tafasitamab and lenalidomide. Decreases in platelets and ANCs have also been observed with plamotamab. These decreases may worsen in grade or duration when the products are given in combination. Monitor blood counts carefully and follow institutional guidelines for the treatment of neutropenia and thrombocytopenia, which may include growth factors and whole blood/blood product transfusions. Management may also include the delay in the administration of study drugs until the counts return to at least Grade 2 levels. See Section 4.7 for any dose modifications to study drugs.

4.6.3.2. Part 2, Arm B (Tafasitamab and Lenalidomide)

Hematologic toxicities have been observed with tafasitamab and lenalidomide. Follow toxicity management instructions provided in the prescribing information for tafasitamab. See Section 4.7 for any dose modifications to study drugs.

4.6.4. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a rare but serious and life-threatening condition arising from rapid release of tumor cellular contents after lysis; resulting metabolic imbalances can lead to acute kidney failure and/or other life-threatening conditions. Subjects with high tumor burden, highly proliferative disease, and/or certain preexisting conditions such as renal disease are at increased risk of TLS.

4.6.4.1. Safety Run-in and Part 2, Arm A (Plamotamab, Tafasitamab and Lenalidomide)

It is unknown whether treatment with plamotamab, tafasitamab, and lenalidomide can cause TLS in R/R DLBCL. The Phase 1 plamotamab monotherapy study in CD20-expressing hematologic malignancies had investigator-reported, any-grade TLS in 4 of 96 subjects (4.2%), of which only 2 of the 80 R/R NHL subjects (2.5%) experienced TLS; importantly, no serious or fatal events of TLS have been reported with plamotamab monotherapy in R/R DLBCL (Plamotamab IB 2021). Likewise, no events of TLS were reported in the Phase 2 open-label, single-arm, tafasitamab plus lenalidomide study in R/R DLBCL (L-MIND) (Duell, 2021). However, fatal instances of TLS have been reported with lenalidomide in other indications and combinations (Revlimid® PI, 2021; Revlimid® SmPC, 2022). All subjects should be assessed for risk of TLS according to institutional practices based on laboratory parameters and tumor bulk prior to initiation of the study medications.

4.6.4.2. Prophylaxis, Monitoring, and Treatment of Tumor Lysis Syndrome

Prophylaxis should be instituted prior to the start of treatment for subjects at high risk for TLS per investigator's assessment. Hospitalization may be considered for subjects considered high risk for TLS per investigator and/or creatinine clearance of < 80 mL/min. Allopurinol (or other xanthine oxidase inhibitors) should be initiated at least 48 hours prior to C1D1 in subjects considered medium to high risk for TLS. Rasburicase is indicated for elevated uric acid levels and monitoring of TLS. During study treatment, all subjects require appropriate laboratory testing prior to administration of study medications including uric acid, potassium, phosphorus, calcium, and

creatinine. Laboratory results should be evaluated in real time. If subjects are not able to consume adequate oral fluids, IV fluids should be added.

If a subject experiences laboratory changes or symptoms suggestive of TLS, treatment with plamotamab, tafasitamab and lenalidomide should be interrupted. Investigators should follow institutional guidelines for treatment of TLS. Study treatment is held until resolution of TLS. If moderate or high risk for TLS remains after resolution, consideration of additional prophylactic measures and/or continued dose interruption or reduction of plamotamab, tafasitamab, or lenalidomide may be considered.

4.6.4.3. Part 2, Arm B (Tafasitamab and Lenalidomide)

Follow the guidelines in Section 4.6.4.2 for the prophylaxis, monitoring, and treatment of TLS.

4.7. Dose Modification Guidelines

Treat subjects experiencing a significant toxicity with standard medical interventions (eg, use of filgrastim to treat neutropenia, acetaminophen for fever) as appropriate. For infusion reactions/CRS and neurotoxicity management, Investigators may use their standard treatment practices, and for additional guidance, see Section 4.6.

In general, if a > Grade 2 toxicity prevents dosing > 14 days and/or if 2 consecutive doses are missed (this applies to weekly and Q2W dosing), the subject may require discontinuation from the plamotamab or tafasitamab treatment. Subjects may reinitiate study drug, even after 2 or more missed consecutive doses of plamotamab or tafasitamab, if the Investigator determines that the benefit outweighs the risk and the toxicity (if applicable) can be controlled by concomitant medication or other means. Medical Monitor approval is required for delays of > 14 days and/or 2 consecutive doses.

During weekly dosing of plamotamab and/or tafasitamab, if a subject's dose is held for ≥ 7 days, it should be considered missed. During Q2W dosing of plamotamab and/or tafasitamab, if a subject's dose is held for ≥ 14 days, it should be considered missed. If a subject's dose is given out of window or delayed for safety concerns, including AEs, it is not considered a protocol deviation.

Plamotamab may be resumed after prolonged dose delay for more than one cycle for reasons other than toxicity (eg, comorbidity, pseudoprogression, or delayed response). Resuming initial treatment course may be allowed on a case-by-case basis if the Investigator and the Sponsor consider this in the best interest of the subject. As a safety measure, the dose may be lowered to the priming dose for re-titration. Study assessments, including local and/or central labs, are to be collected per the Schedule of Assessments.

For toxicities that could overlap (eg, CRS, infusion reaction, hematologic toxicities), detailed dose modifications by grade are presented in Table 8 below:

Table 8: Dose Modifications for Select Toxicities

Adverse Reaction	Severity	Dosage Modification
Infusion-related reactions	Grade 2 (moderate)	• Interrupt infusion of tafasitamab or plamotamab immediately and manage signs and symptoms. • Once signs and symptoms resolve or reduce to Grade 1, resume infusion at no more than 50% of the rate at which the reaction occurred. If the subject does not experience further reaction within 1 hour and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to the rate at which the reaction occurred. • Dosing of other study medications is not modified.
	Grade 3 (severe)	• Interrupt infusion of tafasitamab or plamotamab immediately and manage signs and symptoms. • Once signs and symptoms resolve or reduce to Grade 1, resume infusion at no more than 25% of the rate at which the reaction occurred. If the subject does not experience further reaction within 1 hour and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to a maximum of 50% of the rate at which the reaction occurred. • If the reaction returns after the rechallenge, stop the infusion immediately. • Dosing of other study medications is not modified.
	Grade 4 (life-threatening)	• Stop the infusion immediately and permanently discontinue: – Tafasitamab if during or immediately following tafasitamab infusion. – Plamotamab if during or immediately following plamotamab infusion.
Cytokine release syndrome	Grade 2 (moderate)	• Interrupt plamotamab infusion immediately and manage signs and symptoms (see Section 4.6.1.6). • Once signs and symptoms resolve or reduce to Grade 1, resume plamotamab infusion at no more than 50% of the rate at which the reaction occurred. If the subject does not experience further reaction within 1 hour and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to the rate at which the reaction occurred. • Tafasitamab and lenalidomide dosing is not modified.
	Grade 3 (severe) & Grade 4 (life-threatening)	• Interrupt plamotamab infusion immediately and disconnect infusion tubing from subject. Manage signs and symptoms (see Section 4.6.1.6). • The next scheduled dose of plamotamab will be given at 75% of the previous dose, unless the reaction occurred

Adverse Reaction	Severity	Dosage Modification
		on the C1D1 dose, in which case 100% of the previous dose may be given. • For subsequent plamotamab infusions, if: – Toxicity does not recur or recurs at a Grade 1 severity, escalate to full dose of plamotamab at the time of the next dose. – Toxicity recurs at a Grade 2 severity, maintain 75% dosing of plamotamab. – Toxicity recurs at ≥ Grade 3 severity at any time or if a Grade 2 takes more than 10 days to resolve to ≤ Grade 1, discontinue plamotamab permanently. • Lenalidomide is also modified if a ≥ Grade 3 CRS event occurs: – During the first 5 doses of plamotamab: Reduce current dose of lenalidomide by 10 mg (or to 5 mg if currently at 10 mg) for subsequent doses until C4D1, when lenalidomide may be increased back to the dose prior to CRS. If CRS recurs at ≥ Grade 2 on subsequent reduced dose lenalidomide, permanently discontinue lenalidomide. – After the first 5 doses of plamotamab: Reduce lenalidomide by 10 mg (or to 5 mg if currently at 10 mg) for all subsequent doses. If CRS recurs at ≥ Grade 2 on subsequent reduced dose lenalidomide, permanently discontinue lenalidomide. • Tafasitamab dose is not modified.
Myelosuppression	Platelet count of less than 50,000/μL	• Withhold plamotamab, tafasitamab, and lenalidomide and monitor CBC weekly until platelet count is 50,000/μL or higher. • Resume plamotamab and tafasitamab at the same dose and lenalidomide at a reduced dose. Refer to lenalidomide prescribing information for dosage modifications. • If recurrence, repeat drug withholding and lenalidomide reduction steps until minimal lenalidomide dose is reached per lenalidomide prescribing information. • If recurrence at minimal lenalidomide dose, repeat drug withholding step (first bullet above) then reduce the next scheduled plamotamab dose to 75% of the previous dose.

Adverse Reaction	Severity	Dosage Modification
	Neutrophil count of 1,000/μL or less for at least 7 days OR Neutrophil count of 1,000/μL or less with an increase of body temperature to 100.4°F (38°C) or higher OR Neutrophil count less than 500/μL	• Withhold plamotamab, tafasitamab, and lenalidomide and monitor CBC weekly until neutrophil count is 1,000/μL or higher. • Resume plamotamab and tafasitamab at the same dose and lenalidomide at a reduced dose. Refer to lenalidomide prescribing information for dosage modifications. • If recurrence, repeat drug withholding (first bullet above) and lenalidomide reduction steps until minimal lenalidomide dose is reached per lenalidomide prescribing information. • If recurrence at 5 mg lenalidomide, repeat drug withholding steps then reduce the next scheduled plamotamab dose to 75% of the previous dose.
Febrile Neutropenia	Grade 3 (severe) & Grade 4 (life-threatening)	• Withhold plamotamab, tafasitamab, and lenalidomide and monitor CBC until neutrophil count is Grade ≤ 1. • Once subject is afebrile, off antibiotics and neutrophil count is Grade ≤ 1, resume all therapy at the same dose and schedule.
Neurotoxicity	Grade 3 (severe)	• Withhold plamotamab and manage signs and symptoms (see Section 4.6.1.7) until the toxicity has recovered to ≤ Grade 1 (mild) and has remained at ≤ Grade 1 for at least 3 days before restarting therapy. • Reduce next scheduled plamotamab dose to 75% of the previous dose. If ≥ Grade 2 toxicity does not recur, escalate plamotamab to full dose in subsequent administrations. • If ≥ Grade 2 toxicity recurs at 75% dose, or if < Grade 2 toxicity takes more than 7 days to resolve, permanently discontinue plamotamab. • Tafasitamab and lenalidomide dosing is not modified.
	Grade 4 (life-threatening)	• Stop infusion immediately, if still infusing and permanently discontinue plamotamab.
AST, ALT, bilirubin, and alkaline phosphatase in the absence of CRS	Grade 3 (severe)	• Withhold plamotamab and manage signs and symptoms until the toxicity has recovered to ≤ Grade 1 (mild) or baseline. • If a Grade 3 liver toxicity persists > 14 days and/or 2 consecutive doses are missed and the toxicity cannot be attributed to another cause, permanently discontinue plamotamab. • Tafasitamab and lenalidomide dosing is not modified.
	Grade 4 (life-threatening)	• Withhold plamotamab, tafasitamab, and lenalidomide and manage signs and symptoms until toxicity returns to ≤ Grade 1 (mild) or baseline

Adverse Reaction	Severity	Dosage Modification
		• If a Grade 4 liver toxicity persists > 3 days, permanently discontinue plamotamab, tafasitamab, and lenalidomide
Renal Impairment/failure	Creatinine clearance 59-30 mL/min	• Reduce lenalidomide to 10 mg daily on Days 1-21 of each cycle. • Tafasitamab and plamotamab dosing is not modified
	Creatinine clearance 30 mL/min not requiring dialysis	• Reduce lenalidomide to 15 mg every other day for Days 1-21 of each cycle. • Tafasitamab and plamotamab dosing is not modified
	Creatinine Clearance below 30 mL/min requiring dialysis	• Reduce lenalidomide to 5 mg once daily for Days 1-21 of each cycle. On dialysis days, administer the dose following dialysis. • Tafasitamab and plamotamab dosing is not modified

ALT = alanine aminotransferase; AST = aspartate aminotransferase; C#D#, eg C1D1 = Cycle # Day #; CBC = complete blood count; CRS = cytokine release syndrome.

For other Grade ≥ 3 AEs, other dose modifications will be considered on a case-by-case basis, after discussion between the Sponsor and Investigator.

4.8. Criteria for Study Modifications

Part 1 consists of a 40-subject, two-cohort, single-arm evaluation of the safety of the triple combination. The Sponsor may adjust the dose and/or schedule for Cohort 2 based on the initial safety evaluation of Cohort 1A and 1B. The Sponsor will assess the data from both cohorts to determine the dose and/or schedule before beginning the randomized portion of the study.

4.9. Independent Committees

4.9.1. Independent Data Monitoring Committee

The IDMC will periodically monitor the randomized portion of the study for safety considerations. The IDMC will consist of independent reviewers who are not directly involved in the conduct of the study and will advise the Sponsor of any trends or safety issues which may impact the study and/or the study subjects. The IDMC will operate according to a charter, which the committee will review and ratify before enrollment commences. The IDMC, at a minimum, will as follows:

- Consist of at least 2 oncologists + 1 statistician, all of whom are independent from the study personnel
  - Evaluate accumulating safety data during Part 2 for all enrolled and treated subjects after 50, 100, and 150 subjects have been randomized.

4.9.2. Blinded Independent Review Committee

A BIRC will conduct a blinded review of combined positron emission tomography with computerized tomography (PET/CT) scans or CT scans performed during evaluation of efficacy during the study. An imaging laboratory will conduct the review to document response (CR, PR, stable disease [SD], or progressive disease [PD]) to therapy for all subjects with at least 1 post-baseline disease assessment. The central reviewers will be independent of the study investigators and blinded to study arm assignment. Each efficacy evaluation for every subject will be reviewed by 2 independent radiology reviewers and a clinical reviewer, with any discordance between the radiology reviewers adjudicated by a third radiologist. The committee will operate according to a charter which will be prepared prior to any efficacy analysis.

4.9.3. Independent Confirmation of Histological Diagnosis

A central pathologist will review tissue (archival or fresh) provided at baseline to retrospectively confirm the diagnosis and cell of origin. The pathologist will not be a participating investigator in the study and will operate according to a charter.

5. STUDY ASSESSMENTS

Table 9 defines the timing of study events and assessments, and Table 10 defines the sampling days for plamotamab ADA, cytokines, PK, ECGs, and rituximab levels. Table 11 defines the sampling days for tafasitamab ADA and PK. For additional details, refer to the protocol text and study manuals.

Table 9: Schedule of Assessments

Pretreatment, Cycle 1, and Cycle 2																				
Evaluation or Procedure	**Pretreatment**				**Cycle 1**										**Cycle 2**					
Day	**-35 to -9**	**-8**	**-4**	**-1**	**1**	**2**	**3**	**4**	**8 ± 1**	**9**	**15 ± 1**	**16**	**22 ± 1**	**23**	**1 ± 1**	**2**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**26 ±3**
Informed consent	X																			
Review of inclusion/exclusion criteria	X																			
Inpatient status [a]				X	X	X	X	X	X	X	X	X	X	X	X					
Registration (Part 1)/Randomization (Part 2)	X																			
Plamotamab administration [b, c]					X				X		X		X		X		X	X	X	
Tafasitamab administration [d]		X	X		X				X		X		X		X		X	X	X	
Lenalidomide administration [e]					X	X	X	X	X	X	X	X			X	X	X	X		
Medical History [f]	X																			
Physical examination [f]	X	X		X	X		X		X[g]		X[g]		X[g]		X[g]		X[g]	X[g]	X[g]	X
Neurologic exam, including ASTCT ICANS Consensus Grading [h]	X			X	X	X	X		X		X		X		X		X	X	X	
Vital signs [c, i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
Height	X																			
Weight	X	X		X					X[g]		X[g]		X[g]		X[g]		X[g]	X[g]	X[g]	
ECOG PS	X	X		X	X[g]				X[g]		X[g]		X[g]		X[g]		X[g]	X[g]	X[g]	
CBC w/ differential [j]	X	X		X	X	X	X	X	X[g]	X	X[g]	X	X[g]	X	X[g]		X[g]	X[g]	X[g]	
Chemistry panel [j]	X	X		X	X	X	X		X[g]		X[g]		X[g]		X[g]		X[g]	X[g]	X[g]	
Coagulation panel	X			X		X			X[g]		X[g]		X[g]		X[g]					
Fibrinogen				X		X			X[g]		X[g]		X[g]		X[g]					
Urinalysis with microscopy [k]	X	X		X		X			X[g]		X[g]		X[g]	X	X[g]					
HBsAb, HCV, HIV [l]	X																			
HBsAg, Hepatitis B DNA [m]	X														X					
Urine or serum β–hCG (females of childbearing potential) or serum FSH (postmenopausal) [n]	X	X		X					X[g]		X[g]		X[g]		X[g]					

Pretreatment, Cycle 1, and Cycle 2																				
Evaluation or Procedure	**Pretreatment**				**Cycle 1**										**Cycle 2**					
Day	**-35 to -9**	**-8**	**-4**	**-1**	**1**	**2**	**3**	**4**	**8 ± 1**	**9**	**15 ± 1**	**16**	**22 ± 1**	**23**	**1 ± 1**	**2**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**26 ±3**
LEN Counseling/Dosing Diary Collection	X				X										X					
Rituximab levels				X											X					
Peripheral blood for TBNK, leukocyte flow cytometry [o]	X	X			X	X	X		X	X	X	X	X	X	X	X				
Peripheral blood for RNA analysis [o]		X									X				X					
SARS-CoV-2 nucleic acid or antigen test [p]	X																			
Tumor assessment [q, r]	X																			X
Archival Tissue [s]	X																			
Tumor Biopsies [t]	X												X							
ctDNA Sample [u]	X				X						X				X					X
Monitor/record adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone/email/mail contact for progression/survival																				
12-lead ECG (supine)	X			See Table 10																
Cytokines	See Table 10																			
PK Sampling	See Table 10																			
ADA sampling	See Table 10																			

	Cycles 3 + and Post-Treatment															
Evaluation or Procedure	**Cycle 3**				**Cycle 4**			**Cycle 5 and subsequent odd cycles**		**Cycle 6 and subsequent even cycles**			**Post treatment**			
Day	**1 ± 1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**1 ± 1**	**15 ± 1**	**26 ± 3**	**1 ± 1**	**15 ± 1**	**1 ± 1**	**15 ± 1**	**26 ± 3**	**EOT**	**30 d ± 3 post-EOT**	**90 d ± 10 post-EOT**	**Follow-up Q2 mos. ± 2 weeks**
Informed consent																
Review of inclusion/exclusion criteria																
Inpatient status [a]																
Registration (Part 1)/Randomization (Part 2)																
Plamotamab administration [b, c]	X		X		X	X		X	X	X	X					
Tafasitamab administration [d]	X	X	X	X	X	X		X	X	X	X					
Lenalidomide administration [e]	X	X	X		X	X		X	X	X	X					
Medical History [f]																
Physical examination [f]	X	X[g]	X[g]	X[g]	X[g]	X[g]	X	X[g]	X[g]	X[g]	X[g]	X	X	X		
Neurologic exam, including ASTCT ICANS Consensus Grading [h]	X		X		X			X		X			X			
Vital signs [c, i]	X	X	X	X	X	X		X	X	X	X		X			
Height																
Weight	X	X[g]	X[g]	X[g]	X[g]	X[g]		X[g]	X[g]	X[g]	X[g]		X			
ECOG PS	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]		X[g]	X[g]	X[g]	X[g]		X			
CBC w/ differential	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]		X[g]	X[g]	X[g]	X[g]		X			
Chemistry panel	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]		X[g]	X[g]	X[g]	X[g]		X			
Coagulation panel	X[g]		X[g]		X[g]			X[g]		X[g]			X			
Fibrinogen	X[g]		X[g]		X[g]			X[g]		X[g]			X			
Urinalysis with microscopy [k]	X[g]		X[g]		X[g]			X[g]		X[g]			X			
HBsAb, HCV, HIV [l]																
HBsAg, Hepatitis B DNA [m]	X				X			X		X					X	

	Cycles 3 + and Post-Treatment															
Evaluation or Procedure	**Cycle 3**				**Cycle 4**			**Cycle 5 and subsequent odd cycles**		**Cycle 6 and subsequent even cycles**			**Post treatment**			
Day	**1 ± 1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**1 ± 1**	**15 ± 1**	**26 ± 3**	**1 ± 1**	**15 ± 1**	**1 ± 1**	**15 ± 1**	**26 ± 3**	**EOT**	**30 d ± 3 post-EOT**	**90 d ± 10 post-EOT**	**Follow-up Q2 mos. ± 2 weeks**
Urine or serum β–hCG (females of childbearing potential) or serum FSH (postmenopausal) [n]	X[g]				X[g]			X[g]		X[g]					X	
Lenalidomide Counseling/Dosing Diary Collection	X				X			X		X						X[v]
Rituximab levels					X											
Peripheral blood for TBNK, leukocyte flow cytometry [o]	X							X					X			
Peripheral blood for RNA analysis [o]																
SARS-CoV-2 nucleic acid or antigen test																
Tumor assessment [q,r]							X					X	X[w]		X[w]	
Archival Tissue																
Tumor Biopsies [t]																
ctDNA Sample								X[u]		X[u]			X			
Monitor/record adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X[x]	X[x]	
Record concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Phone/email/mail contact for progression/survival																X
12-lead ECG (supine)	See Table 10															
Cytokines	See Table 10															
PK Sampling	See Table 10															
ADA sampling	See Table 10															

ADA = anti-drug antibodies; ASCTC = American Society for Transplantation and Cellular Therapy; β–hCG = beta human chorionic gonadotropin; CBC = complete blood count; C#D# = Cycle # Day #, eg, C1D1 = Cycle 1 Day 1; CRS = cytokine release syndrome; CT = computerized tomography; ctDNA = circulating tumor DNA; d = day; DICOM = Digital Imaging and Communications in Medicine; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EDC = electronic data capture; EOI = end of infusion; EOT = end of treatment; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg =

hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICANS = immune effector cell-associated neurotoxicity syndrome; IV = intravenous; LEN = lenalidomide; mo = month; PE = physical examination; PET = positron emission tomography; PHI = protected health information; PK = pharmacokinetics; PS = performance score; Q# = every # (eg, Q2 mo = every 2 months); SAE = serious adverse event ; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2 of the genus betacoronavirus; TBNK = T-, B-, and NK cell.

[a] Subjects are required to be admitted as inpatient for 72 hours after the first dose of plamotamab and for a minimum of 24 hours after any dose increase of plamotamab.

[b] Plamotamab will be administered as an IV infusion [redacted].

[c] For subjects who tolerate 4 consecutive infusions of plamotamab at a stable dose and schedule without CRS or an infusion reaction during the infusion or post-infusion observation period, the post-infusion observation period and vital signs assessment may be reduced from 5 hours to 2 hours.

[d] Tafasitamab is administered as a 2 hour IV infusion. On days when both plamotamab and tafasitamab are given, the tafasitamab should be administered before plamotamab with at least 2 hours between the infusions.

[e] Lenalidomide is administered orally once daily in the evening on Days 1 to 21 of each 28-day cycle, up to 12 cycles.

[f] Complete medical history and PE is required at screening. For all the other time points an abbreviated, symptom-directed PE is to be performed.

[g] May be performed the day prior to the plamotamab infusion. Results should be available and reviewed before starting plamotamab infusion.

[h] ASTCT ICANS Consensus Grading for Adults, Table 5 and Table 6, must be completed at least 1 hour post-infusion, but no more than 12 hours post-infusion, on the day of plamotamab infusion. On days when no study drug infusion occurs, the assessments should be completed at approximately the same time each day (approximately 24 hours post-infusion, 48 hours post-infusion, 72 hours post-infusion, etc.). Beginning with Cycle 4, the ASTCT ICANS Consensus Grading assessments are only required on Day 1 of subsequent cycles. ICANS Grading should also be performed if clinically indicated.

[i] Supine or sitting blood pressure and heart rate, body temperature, respiratory rate, and blood oxygen saturation by continuous pulse oximetry. On days of infusions, vital signs coinciding with the plamotamab dosing should be taken predose; 15, 30, and 60 minutes after start of infusion (± 5 minutes); at EOI (± 5 minutes); 15 (± 5 minutes); 30 (± 5 minutes); and 60 (±10 minutes) minutes after EOI; and then hourly for 4 hours (± 15 minutes). Vital signs for the tafasitamab dosing should be taken predose and 30 minutes after EOI (± 5 minutes). All vital signs during infusion should be taken with subject in the same position. The pulse oximetry for blood oxygen saturation level needs to be captured with each vital sign collection; however, pulse oximetry monitoring must be maintained continuously, as practical, throughout the entire admission period for each administration of plamotamab, regardless of inpatient or outpatient status. For more information of management of oxygen saturation of 90% or lower, see Section 4.6.1.4.

[j] If performed on dosing days, the assessment should be performed prior to administration of any study drug.

[k] Urinalysis is required; the microscopy is only required if clinically indicated.

[l] May be performed up to 8 weeks prior to screening.

[m] HBsAg and Hepatitis B DNA repeat testing should be performed only if HBcAb serology is positive and HBsAb serology is negative at screening. Testing for visit Days 1 at Cycle 2 and subsequent cycles should be done 1 to 3 days prior to the Day 1 visit so that results are available prior to the Day 1 dose for the subsequent cycles.

[n] FSH needs only to be performed at screening for suspected postmenopausal women. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks.

[o] Draw prior to study drug administration. In addition, unscheduled samples, if available, may be sent to the designated central laboratory per the laboratory manual for flow and biomarker analysis. The frequency of biomarker collections may be reduced during the study based on emerging data.

[p] SARS-CoV-2 nucleic acid or antigen test, performed locally, is to be completed and resulted within 7 days prior to Day –8.

[q] PET/CT and bone marrow biopsy/aspirate (for subjects with known bone marrow involvement). All studies for the baseline assessment should be performed within 21 days prior to Day -8. After Cycle 12, perform disease assessments every 3 cycles (or Q12 weeks) up to Cycle 36 and every 4 cycles (Q16 weeks) up to Cycle 60. Any unscheduled disease assessment performed in suspicion of progressive disease must be recorded in the eCRF.

[r] PHI-redacted tumor assessments including, but not limited to assessment reports and/or digital imaging files (DICOM) for scans/imaging, blood, and bone marrow biopsy pathology reports are to be provided to support response assessments.

[s] Archival tissue from excisional biopsies of lymph node to be sent to the designated central laboratory as an archival block **(preferred)** or up to 43, if possible, unstained slides. Archival tissue must predate study treatment. If archival tissue is not available or is insufficient, the screening fresh tumor biopsy becomes mandatory to satisfy the inclusion criterion.

[t] Fresh tumor biopsy will be collected at screening up to 21 days prior to Day –8. The on treatment fresh tumor biopsy performed after the fourth dose between the C1D22 and C2D1 visit. Fresh tumor biopsy is strongly encouraged but is optional and requires separate consent. The baseline sample becomes mandatory for study participation if archival tissue is not available to satisfy the inclusion criterion.

[u] The Screening (baseline) sample will come from the submitted archival or fresh tumor biopsy sample to identify malignant clones. Samples of whole blood and plasma will be collected through C2D1; only whole blood will be collected at C2D26, C6D1, C9D1, C12D1 and EOT for the detection and quantification of ID clonotype(s) that were identified from the baseline sample.

[v] Male subjects will be followed for 6 months, and female subjects 8 months following the last dose of study drug to confirm contraceptive use.
[w] Subjects who complete a tumor assessment within the prior 14 days do not have to repeat the EOT tumor assessment. If a subject was removed from study for disease progression and this response data for that applicable visit is adequately documented in EDC, the post-treatment (EOT and 90 days post EOT) tumor assessments do not need to be repeated.
[x] Treatment-related SAEs should be followed up until resolution.

Table 10: Sampling for Plamotamab Anti-Drug Antibodies, Cytokines, PK, and ECGs, and Rituximab Levels

Plamotamab PK, cytokines, and ADA, as well as ECGs, are performed for subjects in Part 1 and subjects randomized to Arm A in Part 2. All times are relative to the plamotamab infusion. On days when tafasitamab and plamotamab are administered, draw predose samples and perform ECG before the start of the tafasitamab infusion.

	Pretreatment	Cycle 1				Cycle 2		Cycle 3		Cycle 4+	Post-treatment	
Study Day	**-1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**EOT**	**30d ±3 post EOT**
Predose	Rituximab level	pPK, Cyto, pADA ECG[a]	pPK, Cyto,	pPK, Cyto	pPK, Cyto,	pPK Cyto, pADA ECG Ritux-imab level	Cyto	pPK Cyto, pADA ECG	Cyto,	pPK[b] pADA[b] ECG[b] Ritux-imab level [h]		
During the Infusion		pPK[c] ECG[c]		pPK[d] ECG[d]								
At the end of the infusion (+/- 10 min)		pPK ECG	ECG		ECG	pPK ECG	ECG	pPK ECG		pPK[b] ECG		
7 hr post infusion (+/- 30 min)		Cyto	Cyto	Cyto	Cyto	Cyto	Cyto[g]	Cyto[g]	Cyto[g]			
24 hr post infusion (+/-2 hr)		Cyto	pPK[e] Cyto	Cyto	Cyto	Cyto	Cyto	Cyto	Cyto			
48 hr post infusion (Day 3)		pPK[f]										
Post-treatment; not timed											pPK pADA	pPK pADA

Cyto = cytokine assays; d = day; ECG = electrocardiogram; EOT = end of treatment; pADA = plamotamab anti-drug antibodies; pPK=plamotamab pharmacokinetics.

[a] ECG in triplicate: obtain three ECGs each separated by 2 minutes on Day 1 only; other ECGs are single studies.

[b] In all even numbered cycles only

[c] 1 hour (±10 minutes) after the start of Day 1 plamotamab infusion

[d] 1.5 hours (±10 minutes) after the start of third plamotamab infusion

[e] 24 hours (±2 hours) after the start of the second plamotamab infusion

[f] 48 hours (±4 hours) after the start of the 1st plamotamab infusion

[g] Cytokine assessment is optional at these timepoints

[h] Required only at Cycle 4 Day 1

Note: Predose pPK and ECG: can obtain up to 2 hours prior to the start of the infusion and can be -5 minutes before or +15 minutes after the end of infusion.

In addition to timepoints from Table 10, cytokines should also be drawn if there is clinical suspicion of CRS at any time and repeated 4 hours later.

In the event of a subject overdose, an unscheduled PK sample should be collected and sent to the designated central lab, if requested by the Medical Monitor.

Note: Rituximab level, PK, ADA, and cytokine samples are to be sent to the designated laboratory, per the laboratory manual, for analysis. All samples should be drawn within the time windows of the designated time and should be labeled with the exact, actual time of sampling.

Table 11: Sampling for Tafasitamab Anti-Drug Antibodies and Pharmacokinetics

Tafasitamab anti-drug antibodies and pharmacokinetics performed in all subjects. All times are relative to the tafasitamab infusion.

	Pretreatment	Cycle 1					Cycle 2		Cycle 3		Cycle 4+	Post-treatment	
Study Day	**-8**	**2**	**9**	**15**	**16**	**23**	**1**	**15**	**1**	**15**	**1**	**EOT**	**30d ±3 post EOT**
Pre-dose	tPK, tADA			tPK			tPK tADA	tPK	tPK tADA	tPK	tPK[a] tADA[a]		
30 min (± 15 min) after end of infusion	tPK			tPK			tPK	tPK	tPK	tPK			
Post-treatment; not timed												tPK tADA	tPK tADA

tPK=tafasitamab pharmacokinetics; tADA = tafasitamab anti-drug antibodies; d = day; ; EOT = end of treatment
For pre-dose tPK and tADA, samples can be obtained up to 2 hours prior to the start of the infusion.
[a] In all even-numbered cycles only.
Note: PK, and ADA samples are to be sent to the designated laboratories, per the laboratory manual, for analysis. All samples should be drawn within the time windows of the designated time and should be labeled with the exact, actual time of sampling.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Subject Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be enrolled in the study:

- Adult (age ≥ 18 years)
- Able to provide written informed consent
- Histologically confirmed diagnosis of DLBCL, NOS, including DLBCL arising from low-grade lymphoma (ie, an indolent pathology such as follicular lymphoma, or marginal zone lymphoma transforming into DLBCL)
- Subjects must have CD20+ and CD19+ lymphoma based on flow cytometric or immunohistochemical evaluation of their most recent biopsy
- At a minimum, archival paraffin embedded tumor tissue (preferred) or unstained slides must be available for retrospective cell of origin determination by a central independent pathologist. Subjects will be consented and may undergo an optional (recommended) biopsy to obtain fresh tumor tissue if a peripheral disease site can easily and safely be accessed. A fresh tumor tissue sample will satisfy this criterion for those subjects who do not have adequate archival tumor tissue; in this case, the fresh tumor biopsy becomes mandatory for participation.
- Subjects must have at least 1 of the following:
  - Relapsed disease after standard therapeutic options, as defined below:
    - Documented PD, according to the Lugano 2014 criteria (Cheson, 2014) after the most recently administered anti-lymphoma regimen
  - Primary refractory DLBCL, defined as follows:
    - Documented persistent disease (less than a complete remission [PR, SD, or PD], according to the Lugano 2014 criteria [Cheson, 2014]) at the completion of first-line therapy, or
    - Progressive disease (according to the Lugano 2014 criteria) within 3 months of completion of first-line therapy
- Subjects must have received at least 1 prior systemic line(s) of therapy, one of which must have included multi-agent chemoimmunotherapy that includes an anti-CD20 monoclonal antibody. DLBCL arising from low-grade lymphoma must have relapsed or refractory disease after at least 2 prior lines of chemoimmunotherapy (at least one of which must have been directed at the DLBCL arising from low grade lymphoma).
- At least 1 bidimensionally measurable disease site. The lesion must have a greatest transverse diameter of ≥ 1.5 cm and greatest perpendicular diameter of ≥ 1.0 cm at

baseline. The lesion must have a positive finding on PET scan (for definition, see Cheson, 2014).

- Subjects who are ineligible for or refuse hematopoietic stem cell transplantation (HSCT). Subjects may be considered ineligible for HSCT for any of the following reasons (Documentation of the reason for a subject's ineligibility must be provided in the subject's source data and electronic case report form [eCRF]):
  - Age
  - Performance status
  - Comorbidities
  - Stem cell mobilization failure
  - Failure of prior transplant
  - Insufficient response to salvage chemotherapy
  - Subject refusal
  - Logistical reasons
  - Other potential reasons not listed above will be considered on a case-by-case basis
- If eligible for CAR-T therapy, subjects must consent to bypassing the approved treatment with demonstrated clinical benefit
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Appendix A)
- Completed vaccination for the SARS-CoV-2 virus prior to study entry is recommended

Laboratory Values

- Subjects must meet the following laboratory criteria at screening:
  - ANC $\geq 1.5 \times 10^9$/L (for subject with bone marrow involvement ANC $\geq 0.5 \times 10^9$/L)
  - Platelet count $\geq 90 \times 10^9$/L (for subjects with bone marrow involvement platelet count $\geq 50 \times 10^9$/L)
  - Total serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Subjects with Gilbert's syndrome or documented liver involvement by lymphoma may be included if their total bilirubin is $\leq 5 \times$ ULN

  - ALT, AST, and alkaline phosphatase ≤ 3 × ULN, or < 5 × ULN in cases of documented liver involvement

  - Serum creatinine clearance must be ≥ 60 mL/minute calculated using a standard Cockcroft and Gault formula or Modification of Diet in Renal Disease (MDRD; Levey, 1999)

- Willingness to avoid pregnancy or fathering children based on the criteria below.

  - Male subjects with reproductive potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 180 days (6 months) after the last dose of study treatment, even if they have undergone a successful vasectomy, and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Section 6.4) should be communicated to the subjects and their understanding confirmed.

  - Women of childbearing potential subjects:
    - Must commit either to abstain continuously from heterosexual sexual intercourse or agree to take appropriate precautions to avoid pregnancy (by using 2 different methods of birth control with at least 99% certainty) starting at least 4 weeks before taking the study treatment, while taking the study treatment, during breaks (dose interruptions), and for at least 8 months after stopping the study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Section 6.4) should be communicated to the subjects and their understanding confirmed.
    - Must have a negative serum pregnancy test at screening (within 10 to 14 days of Day –8) and before the first dose of lenalidomide on Day 1 (within 24 hours of initiating treatment with lenalidomide).
    - Agree to ongoing pregnancy testing during the course of the study: weekly during the first month of study drug treatment, then monthly thereafter for women with regular menstrual cycles or every 2 weeks for women with irregular menstrual cycles (even if true abstinence is the chosen method of birth control) up to and including the end-of-treatment (EOT) visit.
    - Must refrain from breastfeeding and donating oocytes during the course of study and for 8 months after the last dose of study treatment.

Note: The subjects should be informed about the option of donation and cryopreservation of germ cells before the study if applicable.

- In the opinion of the Investigator, the subjects must:

  - Be able and willing to receive adequate prophylaxis and/or therapy for thromboembolic events

  - Be able to understand, give written informed consent, and comply with all study-related procedures, medication use, and evaluations

- Not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative

- Be able to understand the reason for complying with the special conditions of the protocol and supplemental Summary of Pregnancy Prevention Strategies and give written acknowledgement of this in the informed consent form (ICF)

6.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

Exclusionary Diagnosis

- High-grade B-cell lymphoma, including those with MYC and BCL2 and/or BCL6 rearrangements (double-hit or triple-hit lymphoma) and high-grade B-cell lymphoma NOS, according to WHO 2016 criteria

- Any other histological type of lymphoma, including primary mediastinal (thymic) large B-cell (PMBL) or Burkitt lymphoma

- A prior diagnosis of CLL (Richter's Transformation)

- Primary central nervous system (CNS) lymphoma

- A history of secondary CNS involvement by DLBCL are ineligible, unless treated into remission

Exclusionary Previous and Current Treatment

- Subjects who have previously received treatment with an anti-CD20 × anti-CD3 bsAb

- Subjects who have been previously treated with tafasitamab

- Anti-CD20 therapy (eg, rituximab) within 21 days prior to Day –8, in order to minimize competition with plamotamab binding to CD20 on DLBCL target cells

- Subjects who have, within 14 days prior to Day –8:

  - Chemotherapy, radiotherapy, or other lymphoma-specific therapy not including anti-CD20 therapy. Note: palliative local radiotherapy is permitted; however, these lesions may not serve as target lesions.

  - Small molecule or investigational anticancer agents within 6 elimination half-lives prior to Day –8

  - Undergone major surgery not related to lymphoma complications or suffered from significant traumatic injury

  - Received live vaccines (see Section 7.2 for details) within 30 days of Day –8
  - Required systemic anti-infective therapy for active, intercurrent infections

- Subjects who have had the following prior therapies or treatments:
  - Have, in the opinion of the Investigator, not recovered sufficiently from the adverse effects of prior therapy(ies)
  - Were previously treated with CD19-targeted therapy, including CAR-T, unless current biopsy (after last therapy) is CD19+
  - Have known intolerance to CD20 monoclonal antibody therapy
  - Have a history of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, IMiDs, and/or the excipients contained in the study drug formulations
  - Have undergone ASCT ≤ 1 month prior to signing the informed consent form. Subjects who have a more distant history of ASCT must exhibit full hematologic recovery before enrollment into the study.
  - Have undergone previous allogenic stem cell transplantation
  - Have a history of deep venous thrombosis/embolism, threatening thromboembolism, or known thrombophilia, or are at high risk for a thromboembolic event in the opinion of the Investigator, and who are not willing/able to take venous thromboembolic event prophylaxis during the entire treatment period
  - Concurrently use other anticancer or experimental treatments

Exclusionary Subject's Medical History

- Prior history of malignancies other than DLBCL, unless the subject has been free of the disease for ≥ 3 years prior to screening. Exceptions to the ≥ 3-year time limit include a history of the following:
  - Basal cell carcinoma of the skin
  - Squamous cell carcinoma of the skin
  - Carcinoma in situ of the cervix
  - Carcinoma in situ of the breast
  - Carcinoma in situ of the bladder

- Tumor/Node/Metastasis stage of T1a or T1b prostate cancer

- Subjects with the following medical history:
  - Known active hepatitis infection:
    - Positive test for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb; a subject whose HBsAg or HBcAb is positive may be enrolled if a hepatitis B virus [HBV] DNA test is negative and either the subject is treated with potent antiviral therapy or is re-tested for HBV DNA every month)
    - Positive test for hepatitis C virus (HCV) antibodies (a subject whose HCV antibody test is positive may be enrolled if quantitative HCV polymerase chain reaction test is negative)
  - Known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV)
  - Positive SARS-CoV-2 nucleic acid or antigen test
  - History or evidence of clinically significant cardiovascular, CNS, and/or other systemic disease that would in the Investigator's opinion preclude participation in the study or compromise the subject's ability to give informed consent
  - History of solid organ transplantation
  - History or evidence of rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
  - Gastrointestinal abnormalities that would interfere with the ability to take or absorb oral medication

6.3. Subject Withdrawal Criteria

6.3.1. Criteria for Removal from Study Treatment

A subject may withdraw from the study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for any of the following reasons:

- Disease progression
- Occurrence of an unacceptable AE
- Investigator decision
- Subject non-compliance with study drug
- Death

- Administrative reasons
- Other

Subjects must be withdrawn from treatment if the beta human chorionic gonadotropin (β-HCG) pregnancy test is consistent with pregnancy. Before permanent study treatment discontinuation, the treatment may be interrupted to confirm the positive pregnancy test. Pregnancy should be reported as described in Section 10.4. Subjects with a confirmed positive pregnancy test will continue in the follow-up phase of the study.

6.3.2. Criteria for Removal from Study

The subject is considered to be off study for any of the following reasons:

- Screen failure
- Completed study follow-up period of 5 years
- Subject requests to be withdrawn from study and any follow-up
- Death

Whenever possible, the Sponsor must be notified within 24 hours if a subject is withdrawn from treatment and/or study. The reason(s) for a subject's discontinuation from the treatment and study are to be reported to the Sponsor and recorded in the source documents and the subject's eCRF. For subjects who withdraw their consent from the study, this must be clearly documented in their subject source documents with confirmation that no further follow-up and data may be collected.

The EOT and end-of-study (EOS) termination pages in the eCRF must be completed for all subjects who discontinue permanently.

For subjects who discontinue study treatment, all assessments described for the EOT visit should be performed at the scheduled visit dates (if at all possible). Subjects who complete a tumor assessment within 14 days of EOT do not have to repeat the EOT tumor assessment. Complete the EOS eCRF and any follow-up forms at the time of screen failure, death, or withdrawal of consent.

If it is possible, perform all assessments as close to the scheduled dates as is practicable. Post-treatment evaluations should attempt to be completed no later than approximately 4 weeks after the final dose administration and prior to initiation of a new treatment for the malignancy.

Subjects who are withdrawn for any reason may not re-enter this study. The Study Sponsor, Xencor, reserves the right to terminate this clinical study at any time and for any reason.

6.4. Avoidance of Pregnancy

Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be

excluded before start of treatment. Prevent pregnancy during treatment by the use of 2 reliable methods of contraception (USPI, Section 5.1). For the most recent information on lenalidomide, see the prescribing information in Revlimid® PI, 2021; Revlimid® SmPC, 2022.

For the most recent information on tafasitamab , refer to the US PI (Monjuvi® PI, 2021) or the European Medicines Agency SmPc (Minjuvi® SmPC, 2021).

Subjects receiving tafasitamab and/or lenalidomide should refer to their respective medication guides for more information on avoidance of pregnancy.

Female subjects and male subjects with female partners of childbearing potential must agree to use 2 highly effective methods of birth control during, and after, the last dose of study drug. Women are considered to be of childbearing potential unless there is a documented reason (ie, postmenopausal by history with no menses for 1 year and confirmed by follicle-stimulating hormone [FSH; using local reference ranges], OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy (CTFG, 2020).

Male subjects will be followed for 6 months, and female subjects 8 months following the last dose of study drug to confirm contraceptive use. If a pregnancy occurs during this timeframe, it will be reported per guidelines in Section 10.4. A woman is considered of childbearing potential, ie fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by vasectomy or bilateral orchiectomy (CTFG, 2020).

Women of childbearing potential must have a negative serum or urine pregnancy test during screening, prior to starting study therapy at Day –8 and again at Cycle 1 Day 1. In addition, a negative pregnancy test is required at Day 1 of each subsequent cycle prior to study drug infusion, and women of childbearing potential must use a combination of one highly effective contraception and one effective contraception method during the study and for 8 months following last dose of plamotamab, tafasitamab, or lenalidomide (whichever is administered last).

Highly effective contraception includes the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal and transdermal
- Contraception methods that are considered to have low user dependency include the following:
  - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable and implantable

  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
  - Vasectomized partner
- Sexual abstinence
  - Sexual abstinence is considered a highly effective contraception method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. The Investigator is responsible for evaluating the reliability of the subject's ability to maintain sexual abstinence throughout the duration of the clinical trial.

Effective contraception includes the following:

- Male condom
- Diaphragm
- Cervical cap

Periodic abstinence (calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Progesterone-only "mini pills," IUD progesterone T, female condoms, and cervical shield are also not acceptable.

The male subjects must agree to use condoms.

7. TREATMENT OF SUBJECTS

7.1. Dosing Schedule and Premedications

7.1.1. Plamotamab Dosing Schedule and Premedications

Subjects in Part 1 and those randomized to Arm A in Part 2 will be administered plamotamab IV [redacted] In Cycle 1, plamotamab will be administered once every 7 days (± 1 day) for 4 doses; beginning with Cycle 2, plamotamab will be administered every 2 weeks.

Subjects in Cohort 1A and Cohort 1B receive plamotamab according to the doses and schedule in Table 12.

Table 12: Cohorts 1A and 1B Plamotamab Dosing Regimen

Cohort	Dose Level	Cycle 1 Day 1 (Priming Dose)	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22	Cycle 2 Day 1	Cycle 2 Days 1, 8, 15, and 22	Cycle 3 and Subsequent Q2W Dosing
1A	-1	0.8 mg	2 mg	20 mg	20 mg	20 mg	20 mg	20 mg
1B	1	0.8 mg	2 mg	20 mg	35 mg	50 mg	50 mg	50 mg

Q2W = every 2 weeks.

The dose and schedule of plamotamab for Part 2 will be determined in Part 1.

Adjustments may be made to the infusion rate to increase the length of infusion time based on the Investigator's judgement of safety. Due to pump accuracy variations, infusions ending within 5 minutes prior to the required [redacted] period will not be considered a deviation.

Administer plamotamab at least 2 hours after tafasitamab on days when both products are given. All subjects in Part 1 and randomized to Arm A in Part 2 will be premedicated for plamotamab doses as indicated in Table 13.

Table 13: Premedications for Plamotamab

	Cycle 1	Subsequent Cycles
Dexamethasone (if plamotamab alone is administered)	20 mg IV approximately 1 hour prior	Optional
Diphenhydramine	25 mg PO or IV approximately 30 to 60 minutes prior	Required
Acetaminophen	650 mg PO approximately 30 to 60 minutes prior	Required

IV = intravenous; PO = by mouth.

Subjects who have received 4 consecutive infusions at a stable dose and schedule without CRS or infusion reactions may have their premedications modified at the discretion of the Investigator.

In the event of the discontinuation of plamotamab, in the absence of disease progression, and if the subject is still receiving benefit from the study treatment, subjects may continue with other study treatment(s).

7.1.2. Tafasitamab Dosing Scheme and Premedications

All subjects will receive tafasitamab. Priming doses will be administered on Days –8 and –4 of a 1-week run-in period. During the first 3 cycles of the study, tafasitamab will be infused on Day 1, Day 8, Day 15, and Day 22 of each cycle. Thereafter, tafasitamab will be administered on a biweekly (every 14 days) basis, with infusions on Days 1 and 15 of each 28-day cycle until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first

(Table 14). The first infusion of tafasitamab is given at a rate of 70 mL/h for the first 30 minutes; then, the rate is increased so that the infusion is administered within 1.5 to 2.5 hours. All subsequent infusions should be infused 1.5 to 2 hours. Administer prior to plamotamab on days when both products are given.

Table 14: Tafasitamab Dosing Scheme

Day –8 and –4 (Priming Dose)	Cycle 1 Days 1, 8, 15, 22	Cycle 2 Days 1, 8, 15, 22	Cycle 3 Days 1, 8, 15, 22	Cycle 4 and Subsequent Q2W Dosing
12 mg/kg	12 mg/kg	12 mg/kg	12 mg/kg	12 mg/kg

Q2W = every 2 weeks.

Tafasitamab should be administered according to the package insert (Monjuvi® PI, 2021) and by a healthcare professional with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions.

All subjects will be premedicated for tafasitamab doses as indicated in Table 15.

Table 15: Premedications for Tafasitamab

	Day -8 and Day -4	Cycle 1 Day 1	Cycle 1 Days 8, 15, and 22	Subsequent Cycles
Dexamethasone (on days when both tafasitamab and plamotamab are administered)	Not applicable	20 mg IV approximately 30 to 60 minutes prior to the start of tafasitamab	20 mg IV approximately 30 to 60 minutes prior to the start of tafasitamab	Required prior to the start of tafasitamab if infusion-related reaction observed Optional if no reaction
Prednisone or equivalent (if tafasitamab alone is administered)	100 mg IV 30 – 60 minute prior to the start of the infusion	-	100 mg IV 30 – 60 minute prior to the start of the infusion	Required if infusion-related reaction observed Optional if no reaction
Diphenhydramine	50 – 100 mg PO or IV approximately 30 – 60 minutes prior	50 – 100 mg PO or IV approximately 30 – 60 minutes prior	Required if infusion-related reaction observed Optional if no reaction	Required if infusion-related reaction observed Optional if no reaction
Acetaminophen	650 – 1000 mg PO approximately 30 – 60 minutes prior	650 – 1000 mg PO approximately 30 – 60 minutes prior	Required if infusion-related reaction observed Optional if no reaction	Required if infusion-related reaction observed Optional if no reaction

IV = intravenous; PO = by mouth.

On study days when both tafasitamab and plamotamab are administered, administer a single dose of dexamethasone in Cycle 1 prior to the start of the tafasitamab infusion. If plamotamab is held and tafasitamab alone is administered, premedication with prednisone or equivalent is required with the first 3 doses only and subsequently required if infusion-related reaction is observed.

For subjects not experiencing infusion-related reactions during the first 3 infusions, premedication is optional for subsequent infusions. If a subject experiences an infusion-related reaction, administer premedications before each subsequent infusion.

In the event of the discontinuation of tafasitamab, in the absence of disease progression, and if the subject is still receiving benefit from the study treatment, subjects may continue with the other study treatment(s).

7.1.3. Lenalidomide Dosing Scheme

All subjects will receive lenalidomide and self-administer a starting dose of 25 mg oral lenalidomide daily on Days 1 to 21 of each cycle. No more than 21 doses of lenalidomide will be dispensed per cycle. Investigators will follow the package insert or SmPC (Revlimid® PI, 2021; Revlimid® SmPC, 2022) for recommended medications for venous thromboembolic event prophylaxis and dosing modifications. It is recommended that subjects take lenalidomide in the evening about the same time each day, with or without food. Advise subjects to swallow lenalidomide capsules whole with water and not to open, break, or chew them. Treatment with lenalidomide may be modified in a deescalating fashion or discontinued based upon clinical and laboratory findings. Detailed dose modification guidelines to manage hematologic and/or other toxicities are provided in the relevant sections of the protocol.

In the event of the discontinuation of lenalidomide, in the absence of disease progression, and if the subject is still receiving benefit from the study treatment, subjects may continue with the other study treatment(s).

7.2. Concomitant Medications

All medications (including over-the-counter-medications and herbals) and blood products that are administered 21 days prior to start of treatment (Day –8) and throughout subject's participation in the study until the 90-day post-treatment follow-up visit must be recorded in the source document and on the eCRF, including date, time, and dose of administration. Concomitant medications for other medical conditions are permitted as clinically indicated, subject to specific requirements outlined below.

Subjects may not concurrently receive:

- Other experimental therapeutics for their malignancy
- Live viral vaccine within 30 days of Day –8, during treatment, within 60 days of the last dose of plamotamab, or within 90 days of the last dose of tafasitamab

Subjects may receive the following concurrent therapy:

- Antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics, and other medications intended to treat symptoms

- Prophylactic filgrastim may **NOT** be administered after the first dose but may be administered during subsequent dosing in subjects who experience Grade 3 or 4 neutropenia as per the American Society of Clinical Oncology guidelines (Robinson, 2018). If a subject develops neutropenia after the first dose, they may be treated with filgrastim after the second or subsequent dose.

- Subjects who experience CRS should receive aggressive intervention and supportive measures. These may include, but are not limited to, acetaminophen, antihistamines, corticosteroids, IV fluids, bronchodilators, epinephrine, vasopressors, oxygen, and tocilizumab (see Section 4.6 for guidance on management).

- Transfusions such as red blood cells (RBCs) and platelets are permitted if medically indicated. These should be leukocyte-filtered and irradiated to prevent development of transfusion-associated, graft-versus-host disease. All attempts should be made to avoid blood product transfusions on the same day as study drug administration.

- Subjects who experience indigestion, nausea, and/or vomiting may be treated with histamine receptor, type 2 antagonists, or proton pump inhibitors

- Subjects may take vitamins and/or supplements provided they are documented on the medication eCRF

- Subjects may have received hepatitis B reactivation prophylaxis with entecavir, tenofovir, or lamivudine

7.3. Treatment Compliance

The Sponsor or its designee will monitor the study according to ICH GCP guidelines. All intravenous investigational therapy will be prepared and administered at the study site, and complete records of administration doses, times, durations, and supportive therapies will be kept. Lenalidomide for oral use will be provided via a specialty pharmacy in the US or as clinical trial material/investigational medicinal product. An accurate accounting of the dispensing and return of lenalidomide for each study subject will be maintained in source documents or pharmacy drug accountability logs on an ongoing basis by a member of the study site staff. Additionally, if any IMP is lost or damaged or if the study subject misses a dose, this information should be documented in the study subject's EDC and source documents. Subjects will be asked to complete a diary of lenalidomide administration to document compliance with therapy.

7.4. Treatment Assignment, Randomization, and Blinding

Prior to administration of any study therapy, each subject must have completed all screening activities, and the Medical Monitor or designee must review the screening data and provide approval for the subject to start treatment in Part 1 or be randomized into Part 2. All subjects that

sign an informed consent form (ICF), including screen failures, will be entered into the electronic data capture (EDC) system.

In Part 1, subjects will be considered enrolled if they have signed the ICF, if the Medical Monitor or designee has confirmed the eligibility of the subject for entry, and if they have received the Day –8 tafasitamab priming dose. Treatment assignment and Study Subject Number assignment will be done by a Randomization and Trial Supply Management (RTSM/IRT) system.

In Part 2, subjects that have signed the ICF and have eligibility confirmed by the Medical Monitor or designee may be randomized. The initiation of study treatment will occur within 72 hours of randomization. Randomized subjects will start with tafasitamab priming doses on Day –8 and –4. Subjects will be randomized at a 1:1 ratio to the 2 treatment arms, stratified by IPI risk score at baseline (3 to 5 versus 0 to 2), number of lines of prior therapy (1 versus ≥ 2), and primary refractory (yes versus no). A maximum of 36 primary refractory subjects may be enrolled. No blinding is specified due to the potential of CRS with plamotamab and infusion-related reactions with tafasitamab. Randomization is performed by a designated member of the Investigator's staff once the Sponsor has reviewed the eligibility. Treatment assignment and Study Subject Number will be assigned by an RTSM/IRT system. Instructions for registering subjects for treatment and performing randomization will be provided in a separate user's manual.

7.5. Pretreatment Evaluations

Only those subjects who meet all inclusion but no exclusion criteria specified in Section 6 may be enrolled into this study. Prior to the initiation of any on-study testing, including screening testing, the subject must have signed the ICF and received a Subject Screening Number (see Section 7.4) from the EDC system. The pretreatment period lasts for up to 28 days and includes screening evaluations (up to 28 days before the first dose of study drug) and baseline assessments.

See Table 9 for the Schedule of Assessments and Table 10 (plamotamab) for ADAs, cytokines, PK, ECGs, and rituximab levels, and see Table 11 (tafasitamab) for the sampling days for ADA and PK levels.

7.5.1. Screening Evaluations (Up to Day –35)

In Part 1, screening assessments are to be performed during the 28-day window prior to the priming dose of tafasitamab. In Part 2, screening assessments are to be performed within 28 days of randomization.

- Obtain signed informed consent (may be done up to Day –35)
- Review inclusion and exclusion criteria
- Medical history and physical exam (PE)
- Neurologic examination will be assessed using the ASTCT ICANS Consensus Grading for Adults (see Section 4.6.1.7)

- Any cytogenetic information available on the tumor from time of original diagnosis and at transformation (if applicable) should be recorded, including cytogenetics, fluorescent in situ hybridization (FISH) analysis, and sequencing data

- Vital signs (supine or sitting position, including heart rate, blood pressure, temperature, respiratory rate, and blood oxygen saturation by pulse oximetry)

- Height, weight

- ECOG performance status (see Appendix A, Performance Status Scale)

- Electrocardiogram (ECG), standard 12-lead, supine position

- Complete blood count (CBC): RBC, hemoglobin, hematocrit, mean corpuscular volume (MCV), RBC distribution width (RDW), white blood cell (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, myelocytes, promyelocytes; include percent and absolute, if reported) and platelet count

- Chemistry panel (sodium, chloride, potassium, bicarbonate, blood urea nitrogen, creatinine, glucose, uric acid, calcium, phosphorous, total bilirubin, ALT, AST, total protein, albumin, alkaline phosphatase, LDH, as well as serum gamma-glutamyl transferase [GGT], amylase, lipase, ferritin (screening only), and C-reactive protein (screening only)

- Coagulation panel (prothrombin time [PT]/international normalized ratio [INR] and activated partial thromboplastin time [APTT])

- Urinalysis with microscopy (pH, specific gravity, ketones, leukocyte esterase, bilirubin, blood, and protein; microscopy may include RBCs, WBCs, hyaline casts, RBC casts, WBC casts, granular casts, waxy casts [include microscopy findings in EDC only if reported])

- Hepatitis B (HBsAg, HBcAb, and HBsAb) and C (HCV), and HIV screening. These tests may have been performed within the previous 8 weeks.

- If HBcAb or HBsAg is positive, perform hepatitis B DNA testing. If subject is negative, subject may be enrolled if hepatitis B reactivation prophylaxis is initiated with entecavir, tenofovir, or lamivudine

- SARS-CoV-2 nucleic acid or antigen test (to be completed within 7 days prior to Day –8)

- Urine or serum β-hCG pregnancy test for women of childbearing potential performed at screening (within 10 to 14 days of Day –8) and at Day –8 or an FSH test for postmenopausal women. An FSH test only needs to be performed once during screening to confirm that the subject is not capable of becoming pregnant.

- Lenalidomide Counseling is performed during screening prior to Day –8. Please see the supplemental Summary of Pregnancy Prevention Strategies, provided under separate cover, for details.

- The following are to be sent to the central laboratory per the laboratory manual:

  – Peripheral blood for T-, B-, and NK cells (TBNK); leukocyte flow cytometry to assess frequencies of circulating leukocytes; and for leukocyte phenotyping, function, and activation markers

  – Peripheral blood for ctDNA analysis to assess MRD (see Section 8.2.1)

  – Archival blocks (preferred) or unstained slides for cell of origin determination by a central pathologist (see Section 8.2.2.1)

  – Biopsy of disease site. Subjects will be consented and may undergo an optional (recommended) biopsy to obtain fresh tumor tissue (for those subjects with accessible superficial lymphadenopathy that can easily and safely be accessed) (see Section 8.2.2.1 and Section 8.2.2.2).

- Tumor assessments will be performed by the Investigator using PET/CT or CT scans and bone marrow if bone marrow involvement is suspected or known. The same evaluations (ie, imaging, blood, bone marrow) performed at baseline will be performed at each subsequent disease assessment. All tumor assessments should be performed within 21 days prior to the first dose of Study Drug (Day –8). Tumor assessments must be read locally, and scans and other relevant information must be submitted to the central imaging designee for review by the BIRC. Redacted tumor assessments including, but not limited to, assessment reports and/or actual data (Digital Imaging and Communications in Medicine [DICOM] files) for scans, blood analysis, and bone marrow biopsy pathology reports may be requested by the Sponsor. If requested by the BIRC, additional information may be required, including the interpretation, differential, and addenda when available (flow cytometry, cytogenetics, FISH, and/or molecular testing.)

- Record AEs and concomitant medications

- During Part 1 and 2, registering a subject for approval by Sponsor and during Part 2, randomization on Day –10/–9 via third party RTSM/ IRT system by a designated member of the Investigator's staff once all eligibility criteria have been verified

7.5.2. Day –8, Day –4, and Day –1

- Abbreviated PE (Day –8 and Day –1 only)

- Neurologic examination will be assessed using the ASTCT ICANS Consensus Grading for Adults (Day –1 only, see Section 4.6.1.7)

- Vital signs (supine or sitting position, including heart rate, blood pressure, temperature, respiratory rate, and blood oxygen saturation by continuous pulse oximetry)
- Weight (Day –8 and Day –1)
- ECOG performance status (see Appendix A)
- CBC with differential (percent and absolute) and platelet count (see Section 7.5.1) (Day –8 and Day –1 only)
- Chemistry panel (see Section 7.5.1) (Day –8 and Day –1 only)
- Fibrinogen (Day –1 only)
- Coagulation panel (PT/ INR and APTT) (Day –1 only)
- Urinalysis (see Section 7.5.1) (Day –8 and Day –1 only)
- Urine or serum β-hCG pregnancy test for women of childbearing potential (Day –8 and Day -1 only)
- The following to be sent to the central laboratory per the laboratory manual:
  - Serum sample for rituximab level (Day –1 only)
  - Serum samples for tafasitamab PK and ADA (Day –8 only)
  - Peripheral blood for TBNK, leukocyte flow cytometry (Day –8 only)
  - Peripheral blood for RNA analysis (Day –8 only, prior to tafasitamab dose)
- Administration of tafasitamab on Day –8 and Day –4
- Record concomitant medications and AEs

7.6. Treatment Evaluations

7.6.1. Treatment Cycles

The schedule of required procedures and clinical site study days for each cycle is detailed in Table 9, Table 10, and Table 11. The day prior to C1D1 is Day -1. Subjects in Part 1 and subjects randomized into Arm A of Part 2 will be admitted to an inpatient facility and monitored for a minimum of 72 hours following dosing for the first dose of plamotamab and for 24 hours following any subsequent dose escalation.

After discontinuation of treatment, subjects will be followed for PFS and OS every 2 months by telephone, email, or mail contact by the site up to 5 years or until death.

Study days for required procedures are specified in the Schedule of Assessments (Table 9). The procedures include the following:

Clinical Assessments: Clinical assessments include the following:

- Abbreviated (study-related) medical history
- PE, including weight and tumor assessment (examination of skin, head, eyes, ears, neck, and throat [HEENT], bidimensional measurement of cervical, supraclavicular, axillary, and inguinal lymph nodes, spleen size [below costal margin], heart, chest, lungs, abdomen, extremities, neurologic, and back).
- Neurologic examination will be assessed using the ASTCT ICANS Consensus Grading for Adults (see Section 4.6.1.7)
- Vital signs (supine or sitting position, including blood pressure, heart rate, respirations, temperature, and blood oxygen saturation by continuous pulse oximetry)
  - For tafasitamab infusion, vital signs and clinical assessment for AEs are monitored during and after the end of the infusion. Timepoints include the following: predose and 30 (± 5) minutes after end of infusion (EOI).
  - For plamotamab infusion, vital signs and clinical assessment for AEs are monitored for a minimum of 5 hours after the end of the infusion. Timepoints include: predose; approximately 15, 30, and 60 minutes after start of plamotamab infusion (± 5 minutes); at end of infusion (± 5 minutes); approximately 15 (± 5) minutes; 30 (± 5) minutes; 60 (± 10) minutes after EOI; and then hourly for 4 additional hours (all windows ± 15 minutes). The pulse oximetry for blood oxygen saturation level needs to be recorded with each vital sign collection; however, pulse oximetry monitoring must be maintained continuously, as practical, throughout the entire admission period for each administration of plamotamab, regardless of inpatient or outpatient status. For subjects who tolerate 4 consecutive infusions of plamotamab at a stable dose and schedule without CRS or an infusion reaction during the infusion or post-infusion observation period, the post-infusion observation period and vital signs assessment may be reduced from 5 hours to 2 hours.
- ECOG performance status (see Appendix A, Performance Status Scale).
- Supine ECG, standard 12-lead (see the Schedule of Assessments [Table 9] for timing of collections, and as clinically indicated). Triplicate ECG at C1D1 only, prior to the Plamotamab infusion. All ECG tracings will be submitted electronically to the Sponsor either by file transfer or scanning the original tracing. Additional details will be provided in a separate manual.
- Lenalidomide Counseling is performed on Day 1 of each cycle. Please see the supplemental Summary of Pregnancy Prevention Strategies, provided under separate cover, for details.

- Record concomitant medications
- Record AEs (CTCAE and CRS revised grading system)
- Tumor assessments will be performed as outlined in Section 9 after Cycle 2, then at the end of even-numbered cycles up to Cycle 12, then every 3 cycles up to Cycle 36, and then every 4 cycles up to Cycle 60, and at EOT.

Laboratory Assessments: Safety laboratory assessments, including CBC with differential, chemistry panel, fibrinogen, coagulation panel, urinalysis, and pregnancy tests, may be completed up to 24 hours prior to the visit day. Excepted is the pregnancy test prior to the first dose of lenalidomide, which should be completed on Cycle 1 Day 1, within 24 hours of initiating treatment. Safety laboratory values, except for differential counts, fibrinogen, coagulation panel, and urinalysis, should be reviewed before starting study drug infusion.

- CBC with differential (absolute and percent), platelet count, and blast count, if reported (see Section 7.5.1)
- Chemistry panel (see Section 7.5.1)
- Fibrinogen
- If HBcAb serology is positive, HBsAg and hepatitis B DNA testing should be performed, with results available prior to dosing, on Day 1 of Cycles 2 and later, and at EOT (unless HBsAb is also present).
- Coagulation panel (prothrombin time PT/INR and APTT)
- Urinalysis (see Section 7.5.1)
- Urine or serum β-hCG pregnancy test for women of childbearing potential should occur weekly during the first 4 weeks of lenalidomide, then on Day 1 of each subsequent cycles for dosing of plamotamab, tafasitamab, or lenalidomide. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks during each subsequent cycle.
- The following are to be sent to the central laboratory per the laboratory manual:
  - Serum samples for plamotamab and tafasitamab ADA, cytokines, and plamotamab and tafasitamab PK (see Table 10 and Table 11 for collection schedule). All samples should be drawn within the window indicated on Table 9 and of the designated time and should be labeled with the exact, actual time of sampling.
  - Peripheral blood for TBNK, leukocyte flow cytometry
  - Peripheral blood for RNA analysis

- Peripheral blood for ctDNA analysis
- Tumor biopsies (for those subjects who provided consent) collected once at follow-up (See Section 8.2.2 and Table 9)

7.6.2. End of Treatment Visit

Subjects will have their EOT visit at the end of the last cycle of treatment. If a subject terminates before the end of a cycle, the EOT assessments (as indicated in Table 9) will be performed as early as possible after study drug discontinuation. Subjects who complete a tumor assessment within 14 days of EOT do not have to repeat the EOT tumor assessment.

7.6.3. Ninety (90) Days After the Last Dose of Study Medication

Subjects will have a visit 90 days after the last dose of any study medication (± 10 days). Efforts should be made to have subjects complete the 90-day post last treatment visit for safety evaluation. The visit is not necessary if the subject enrolls into another trial, if the subject begins treatment for the malignancy under study, or if hospice or palliative care is initiated before this visit; if possible, this visit should be scheduled earlier. Assessments are as indicated in Table 9.

7.6.4. Long-Term Follow-Up Period

All subjects will be followed for progression and OS approximately every 2 months (± 2 weeks) after the 90-day follow-up visit (see Section 7.6.3) visit. This includes subjects who discontinue treatment due to progression or toxicity, as well as those who discontinue before progression to pursue a new anti-lymphoma/salvage therapy (chemotherapy, SCT, radiotherapy, etc.). Subjects who discontinue due to toxicity and without progression will continue to have efficacy assessments performed until progression or the initiation of new therapy. Subjects will be contacted by telephone, email, or mail contact by the site until death or 5 years from randomization. The following data will be collected at each follow-up contact:

- Survival status date and cause of death (if applicable)
- Transplantation date and other transplant related outcomes (if applicable)
- Date of progression
- subsequent treatments and efficacy outcomes of those treatments
- date of last confirmation of survival (last know date alive)

It is anticipated that the information will be available from the treating Investigator, oncologist, primary care physician, local medical records, or the subject. The Investigator may search public sources for status information. Completion of the long-term follow-up period is required for any randomized subject, even if the subject did not receive the intervention. The duration of follow-up on this trial may be modified based on observed subject outcomes, ie, lengthened if significant numbers of durable responses are seen or shortened if few subjects require long follow-up.

7.7. Study Drug

7.7.1. Plamotamab (XmAb13676)

Plamotamab (XmAb13676) is a humanized bsAb that binds both CD3 and the tumor antigen CD20 in order to recruit cytotoxic T cells to kill CD20 positive tumor cells. IV Solution Stabilizer (IVSS) is a concentrated form of the plamotamab (XmAb13676) buffer that also minimizes protein binding to the administration equipment when plamotamab is administered at lower concentrations.

[redacted] Dilution instructions for any alternate fill volumes required during the study will be provided in the pharmacy manual.

[redacted]

7.7.2. Tafasitamab-cxix (Tafasitamab)

Tafasitamab-cxix (herein referred to as tafasitamab) for injection is supplied as a 200 mg vial containing a sterile, preservative-free, white to slightly yellowish lyophilized powder in a single-dose vial for IV use after reconstitution. After reconstitution with 5 mL of Sterile Water for Injection, USP, the resulting concentration is 40 mg/mL with a pH of 6.0. Each single-dose vial contains 200 mg tafasitamab, citric acid monohydrate (3.7 mg), polysorbate 20 (1 mg), sodium citrate dihydrate (31.6 mg) and trehalose dihydrate (378.3 mg).

7.7.3. Lenalidomide

Lenalidomide may be provided by the Investigator or as clinical trial material/investigational medicinal product (Revlimid or regionally approved generic lenalidomide).

7.8. Study Drug Storage

7.8.1. Plamotamab

Vials containing plamotamab and IVSS must be stored under refrigeration at [redacted] in an appropriately secured area accessible only to the pharmacist, the Investigator, or a duly designated person. Since plamotamab does not contain preservatives, opened vials of plamotamab must be used within 24 hours.

7.8.2. Tafasitamab

Vials containing tafasitamab are to be stored according to package insert or SmPC (Monjuvi® PI, 2021; Minjuvi® SmPC, 2021).

7.8.3. Lenalidomide

Lenalidomide is to be stored according to the package label for Revlimid or generic lenalidomide (Revlimid® PI, 2021; Revlimid® SmPC, 2022).

7.9. Study Drug Preparation

7.9.1. Plamotamab

Note that plamotamab has pharmacodynamic effects in vivo at very low concentrations and therefore each product vial must be highly diluted before administration.

Plamotamab solution is prepared under aseptic conditions. Prior to administration, plamotamab will be diluted to the required final concentration in one or more infusion bags containing [redacted]. Prior to dilution, the vial containing parenteral drug product should be inspected visually. If particulate matter and/or discoloration are noted, drug should not be administered, and the Sponsor should be notified. After dilution, the bag containing plamotamab (XmAb13676) should be gently inverted 2 to 3 times to mix the solution. **THE BAG MUST NOT BE SHAKEN**. See the Study Pharmacy Manual for additional details.

7.9.2. Tafasitamab

Tafasitamab is prepared according to the package insert or SmPC (Monjuvi® PI, 2021; Minjuvi® SmPC, 2021).

7.9.3. Lenalidomide

Lenalidomide is provided as orally administered capsules, which the study center will dispense to the subject.

7.10. Study Drug Administration

7.10.1. Plamotamab

Plamotamab has previously been given to humans in a Phase 1 clinical study (XmAb13676-01). In the XmAb13676-01 study, CRS was frequently observed, especially with the Cycle 1 Day 1 dose (Section 2.4). Either a Principal Investigator or Sub-Investigator (MD) must be readily available during and for a minimum of 24 hours after administration of a plamotamab dose.

All subjects will be premedicated in Cycle 1 with dexamethasone 20 mg IV approximately 30 to 60 minutes prior to the start of the tafasitamab infusion. During Cycle 1, if tafasitamab infusion is held for any reason, dexamethasone will be given 1 hour prior to the start of the plamotamab administration. After Cycle 1, premedication with dexamethasone is not required and is permitted at the Investigator's discretion. (Cetirizine or other antihistamine may be used in place of diphenhydramine).

Plamotamab administration should begin as soon as possible after the dosing solution is prepared. If there is a delay in administration, it may be stored at [redacted].

Plamotamab SHOULD NOT BE ADMINISTERED AS AN IV PUSH OR BOLUS.

Study drug will be administered as an open-label solution at a [redacted] using a dedicated infusion set. Precautions for CRS or infusion reactions/anaphylaxis should be observed during plamotamab administration. Due to the possibility that CRS or allergic/infusion reactions may occur, emergency resuscitation equipment (a "crash cart") and medications including steroids and tocilizumab should be present in the immediate area where subjects are receiving their infusions. Additional supportive measures should be available and may include, but are not limited to, acetaminophen, antihistamines, corticosteroids, IV fluids, bronchodilators, epinephrine, vasopressors, and oxygen.

Management of CRS and other infusion-related reactions will be per standard investigational site procedures, or alternatively, as outlined in this protocol. Please refer to Section 4.6 for management of infusion reactions/CRS and neurotoxicity, if needed.

Vital signs will be measured and recorded as described in Section 7.6.1.

7.10.2. Tafasitamab

Tafasitamab will be administered according to the package insert or SmPC (Monjuvi® PI, 2021; (Minjuvi® SmPC, 2021).

7.10.3. Lenalidomide

Lenalidomide will be dispensed to the subject to take orally in the evening according to the package insert or SmPC (Revlimid® PI, 2021; Revlimid® SmPC, 2022). The subject will be given a diary to record the date and time of each administration of lenalidomide and to provide accountability of the product.

If a subject misses a dose of lenalidomide and it is within 12 hours of their normal dosing time, the subject should be instructed to make up the missed dose, and to then take their next dose according to their regular schedule.

7.11. Study Drug Accountability, Handling, and Disposal

Detailed instructions and procedures for study drug dispensing are included in the Pharmacy Manual.

Accurate accounting of all study medication must be maintained. The Investigator agrees to keep an inventory of study drugs using local investigational pharmacy drug accountability logs. Drug disposition records must be kept in compliance with applicable guidelines and regulations.

Upon completion or termination of the study, any used vials, partially used vials, unused study medication, unused diluted drug dosing solutions, or unused IVSS should be destroyed in

Any unused lenalidomide must be returned to the study center for accountability and destruction according to local regulations or institutional policy.

Subjects will be required to keep a diary of the administration of lenalidomide. Dosing instructions will be provided to the subject. Compliance with study intervention will be assessed at the beginning of each cycle. Compliance will be assessed by counting returned capsules, in conjunction with subject diary information and subject questioning and counseling during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of lenalidomide capsules dispensed to and taken by each subject must be maintained and reconciled with study medication and compliance records. Lenalidomide start and stop dates, including dates due to delays and/or dose reductions, will also be recorded in the eCRF.

8. PHARMACOKINETIC, PHARMACODYNAMIC, AND BIOMARKER ASSESSMENTS

8.1. Serum Assessments for Pharmacokinetic Analyses, Anti-Drug Antibodies, Cytokines, and Rituximab Levels

Venous blood samples for serum analyses of plamotamab and tafasitamab PK, plamotamab and tafasitamab ADA, cytokines, and rituximab levels will be obtained as per the schedule listed in Table 10 and Table 11. Remaining samples will be stored for additional testing of biomarkers associated with pharmacodynamic activity, clinical response, or resistance to the study drugs. This testing may occur at ICON Laboratory Services, Inc. or at another Sponsor designee as detailed in the Laboratory Manual.

8.2. Pharmacodynamics and Biomarker Assessments

8.2.1. Peripheral Blood Assessments

Blood specimens will be collected to explore pharmacodynamic effects of plamotamab, tafasitamab, and lenalidomide on leukocyte frequencies and markers of T-cell and/or leukocyte function, including, but not limited to, checkpoint molecules, markers of proliferation and T-cell activation, and markers of T-cell exhaustion. The frequencies of circulating T cells, B cells and NK cells will also be monitored. Additional blood samples will be drawn into PAXgene RNA tubes and stored for potential explorative studies of leukocyte function and pharmacodynamic effects by RNA sequencing and transcriptomic gene and pathway analysis. Baseline and pharmacodynamic markers in the periphery will be evaluated for correlation with incidence of CRS and AEs along with clinical response and resistance. Assessment of CRS in the 24 hours following each dose will include monitoring serum cytokines and flow cytometric evaluation of the change in the quantity and activation state of T cells in the peripheral blood.

A blood sample will be collected at screening and on treatment for measurement of ctDNA. By tracking levels of and mutations in ctDNA by DNA sequencing methods on treatment, ctDNA as a

measure of MRD will be explored as a marker of clinical response. Blood samples may also be used to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.

Detailed instructions for processing and shipping peripheral blood samples are provided in the Laboratory Manual. For the sampling schedule, see Table 9 (Schedule of Assessments). Unscheduled samples may be collected and sent to the designated central laboratory at the discretion of the Investigator. Remaining peripheral blood mononuclear cells, plasma samples, and serum samples will be stored at the designated central laboratory and may be used for assessment of additional future exploratory biomarkers associated with pharmacodynamic activity, clinical response, or resistance to the study drugs.

8.2.2. Tumor Biopsies

8.2.2.1. Archival Tissue

Archival blocks (preferred) or unstained slides will be requested from lymph node biopsies to confirm DLBCL diagnosis, determine cell of origin status, and to perform genomic mutation analysis. Cell of origin assays (COO), germinal center B-cell (GCB), or activated B cell type (ABC) origin will be determined using transcriptional analysis, Nanostring LymphC2x, or other gene expression methods. Immunohistochemistry analysis will be performed using relevant markers in the Hans algorithm (Yoon, 2017).

Archival tissues of diagnostic tumor mass or lymph node must be confirmed to be available at the time of study entry and will be collected and sent to the designated central laboratory within 8 weeks of first dose of study medication or randomization. For the sampling schedule, see Table 9 (Schedule of Assessments). If archival tissue is not available, a fresh tumor biopsy at baseline will be requested (Section 8.2.2.2).

8.2.2.2. Baseline and On-Treatment Tumor Biopsies

Baseline Biopsies: Fresh tumor biopsies (excisional or core needle biopsies) are encouraged as they allow an unbiased analysis of tumor status in contrast to archival biopsies which may not reflect impact of therapies prior to study start. Therefore, pretreatment baseline biopsies will be requested if the subject provides consent and presents with accessible involved lymph nodes, for instance, superficial lymphadenopathy, enabling low-risk procedures to be performed to obtain tissue. Excisional or core needle biopsies are acceptable while fine needle aspiration is not acceptable.

On-treatment Biopsies: On-treatment biopsies are requested in subjects with accessible lymphadenopathy. On-treatment biopsies are to be obtained in the fourth week of treatment (after the C1D22 dose, but prior to the C2D1 dose). In responding subjects, an additional biopsy is recommended upon progression to ascertain the molecular and cellular basis of progression, and to specifically rule out loss of CD19 or CD20 expression as a mechanism of acquired resistance.

Tumor tissue from archival, pretreatment, on-treatment and progression biopsies will be processed to enable analysis, including, but not limited to, (1) DNA sequencing to identify acquired genetic

variants in tumor cells; (2) RNA analysis of tumor and the tumor microenvironment; (3) immunostaining of the tumor for CD19 and CD20 expression, and of the inflammatory cells, including T cells, in the microenvironment.

Baseline and on-treatment biopsies will be collected and sent to the central laboratory designated in the Laboratory Manual. For the sampling schedule, see Table 9 (Schedule of Assessments).

Following the study specified tumor biopsy analysis, remaining archival and fresh biopsy samples will be stored at the designated central laboratory for assessment of additional future exploratory biomarkers associated with pharmacodynamic activity, clinical response, or resistance to the study drugs.

9. ASSESSMENT OF EFFICACY

9.1. Efficacy Assessments

Table 16: Assessment of Response

Response	Site	PET-CT–Based Response	CT-Based Response
Complete	Lymph nodes and extralymphatic sites	Complete metabolic response Score 1, 2, or 3[a] with or without a residual mass on 5PS[b]	Complete radiologic response (all of the following) Target nodes/nodal masses must regress to < 1.5 cm in LDi No extralymphatic sites of disease
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Lymph nodes and extralymphatic sites	Partial metabolic response Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size	Partial remission (all of the following) > 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

Table 16: Assessment of Response (Continued)

Response	Site	PET-CT–Based Response	CT-Based Response
Stable or No response	Target nodes/nodal masses, extranodal lesions	No metabolic response Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	Stable disease < 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	Individual target nodes/nodal masses Extranodal lesions	Progressive metabolic disease Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	Progressive disease requires at least 1 of the following PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by > 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	Non-measured lesions	None	New or clear progression of preexisting non-measured lesions

Response	Site	PET-CT–Based Response	CT-Based Response
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; 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.

Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Recently biopsied lesions should not be used as a measured dominant lesion.
Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

[a] In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).
[b] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

The Investigator and the BIRC will assess response to study drug at each efficacy timepoint. The following endpoints will be reported:

Progression-free Survival: defined as the time from randomization to the first documentation of progressive disease or death, whichever comes first. The Investigator and the BIRC will determine the progressive disease event in all randomized subjects.

Duration of Response: defined as the time from the first response (CR or PR) to progression or death due to any cause among subjects achieving a CR or PR and among CR subjects. DOR will be derived using disease progression as determined by the BIRC in subjects who have a response (CR or PR).

Overall Survival: defined as the time from randomization to death from any cause. All randomized subjects will be followed for up to 5 years for survival.

Time to Treatment Failure: defined as the time from randomization to discontinuation of all study treatment for any reason, including disease progression, treatment toxicity, and death. The time to treatment failure will be using disease progression as determined by the Investigator and by the BIRC.

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

Safety assessments will include the following:

- AEs/SAEs
- Vital signs
- PE findings
- Clinical laboratory safety assessments
  - Note: Information on cytokines associated with CRS will also be collected as additional safety information but will not be assessed in real time.
- ECG parameters
- Performance status (ECOG) changes

10.1.1. Treatment/Reporting of Overdose or Medication Errors

In the event of an overdose, the Investigator should do the following:

- Contact the Medical Monitor immediately

- Closely monitor the subject for any AE/SAE and laboratory abnormalities
- Obtain a plasma PK sample if requested by the Medical Monitor (determined on a case-by-case basis)
- Document the quantity and duration of the excess dose or error

The Investigator, in consultation with the Medical Monitor, will decide dose interruptions or modifications based on clinical evaluation of the subject.

All overdose cases should be reported as SAEs.

10.2. Adverse Events and Serious Adverse Events

10.2.1. Definition of Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a study subject. The AE does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug. Adverse events may include the onset of new illness and the exacerbation of preexisting conditions.

Adverse events are classified as "serious" and "non-serious" for regulatory reporting purposes.

10.2.2. Definition of Serious Adverse Events

A **Serious Adverse Event** (SAE) is an AE occurring during study after the subject has signed the ICF **that fulfills one or more of the following**:

- Results in death
- Is life-threatening; this means that the subject was at immediate risk of death at the time of the event. It does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation in existing hospitalization
  - Note: Hospitalization is defined as more than 24 hours as an inpatient, or prolongation of planned hospitalization by >24 hours due to an AE.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is an important medical event. Important medical events are events that may not be immediately life-threatening but are clearly of major clinical significance in the opinion of the Investigator. They may jeopardize the subject and may require intervention to

prevent one of the other serious outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures that do not result in subject hospitalization, and the development of drug dependency or drug abuse.

A distinction should be drawn between serious and severe (Grade 3) AEs. Severity (see Section 10.2.3.1) is a measure of intensity, whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring hospitalization for monitoring purposes would be considered an SAE but is not necessarily a severe (Grade 3) SAE. Similarly, an AE that is severe (Grade 3) is not necessarily an SAE. For example, alopecia may be assessed as severe (Grade 3) but would not be considered an SAE.

The following should not be reported as an AE/SAE:

- Signs/symptoms and conditions related to disease progression of the primary condition under the investigation (eg, tumor-related pain, metastasis, new lesions, etc.), hospitalization, and death due to disease progression unless related to study drug.

- Hospitalizations for planned surgical/medical elective procedures or planned admissions for study drug administration.

Suspected Unexpected Serious Adverse Reaction (SUSAR):

During the study, the Sponsor may determine that certain safety reports are required to comply with regulations. The Investigator may receive notification of a Suspected Unexpected Serious Adverse Reaction (SUSAR). These reports must be submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) per local requirements as soon as possible, and documentation of this submission should be available to the Sponsor or ICON.

10.2.3. Adverse Event Monitoring, Recording, Reporting, Follow-up, and Assessments

AE monitoring will begin upon the signing of the ICF. Concomitant illnesses, which existed prior to entry into the clinical study, will not be considered AEs unless they worsen during the treatment period. Preexisting conditions will be recorded as part of the subject's medical history. A preexisting condition should be recorded as an AE if the frequency, intensity, or character of the condition worsens during the study period.

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved or stabilized, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Sponsor medical representative, until there is a satisfactory explanation for the changes observed, or until the subject is lost to follow-up.

AEs may be volunteered spontaneously by the study subject, discovered by the study staff during physical examinations, or by asking an open, nonleading question such as "How have you been feeling since you were last asked by us?" or "Have you had any new or changed health problems since you were last here?"

All AE terms (also called reported term or verbatim) should be **recorded** individually. Only a diagnosis, if known, should be recorded as an AE term rather than each individual symptom. If a diagnosis is not available or unclear, all symptoms should be reported.

The recording of AEs will be done in the following manner:

Non-serious AEs will be recorded in the EDC database after signing the ICF through 90 days after the last dose of any study treatment. For screen failed subjects, the recording of non-serious AEs, after the ICF was signed, is not needed.

Serious AEs or SAEs will be recorded in the EDC AE page (eCRF) and the completed SAE report form will be emailed to ICON PVSS. The **Investigator is responsible, within 24 hours of becoming aware of the SAE,** to complete all required details on the initial SAE report form and to email to [redacted]

If new information becomes available or details are changed, the submitted SAE form should be retained at the site as is, and a new (blank) follow up SAE report form for the same case should be completed, marked as "follow-up," and emailed to [redacted] The changes reported in the follow-up SAE report form should be also made in EDC.

Table 17 defines the windows for capturing serious and non-serious AEs.

Table 17: Investigational Site Recording/Reporting of Adverse Events

Type of Adverse Event	Start of Reporting Window	End of Reporting Window
Non-serious AE	**Signing of ICF** Note: If the subject has failed screening, non-serious AEs should not be recorded.	For non-serious AEs: Any of the following would be considered as the end of reporting: • 90 days after the last dose • initiation of another anticancer therapy • withdrawal of consent by subject
SAE	**Signing of ICF**	• 90 days after the last dose • initiation of another anticancer therapy • withdrawal of consent by subject SAEs related to study drug should be followed up until the resolution, if possible.

AE = adverse event; ICF = informed consent form; SAE = serious adverse event.

ICON PVSS may request clarification of omitted or discrepant information from the initial notification or follow-up SAE report as needed. ICON PVSS and/or the Sponsor may also request additional information regarding the SAE in order to obtain the full clinical picture. The Investigator

or an authorized delegate is responsible for providing the requested information in a Data Clarification Form (DCF) to ICON PVSS/Sponsor.

Initial reports of SAEs must be followed up as soon as possible with detailed information; this may include clear photocopies of other documents as necessary (eg, hospital records, consultant reports, autopsy reports, etc.) with the study subject's personal identifiers redacted. All relevant information obtained by the Investigator through review of these documents will be recorded and forwarded to ICON PVSS within 24 hours of receipt of the information.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

E-mail: [redacted]

Fax number: [redacted]

Emergency contact number: [redacted] (within US)

[redacted] (toll number and outside of US)

1. E-mail your SAE report form to the e-mail address above.
2. Provide the name of the Principal Investigator, your name, the telephone number where you can be reached and the protocol number and title.
3. Immediately forward the SAE report form and any supporting documentation to ICON PVSS; this must be done within 24 hours of becoming aware of the event.

The Investigator is responsible for reporting adverse drug reactions (ADRs) related to the other study treatments to the Sponsor. The Sponsor will report the ADRs to the respective Marketing Authorization Holders, as applicable.

Investigators should perform the following assessments of AEs (both for non-serious and serious):

10.2.3.1. AE Severity/Intensity Grading

The Investigator will assess all AEs for severity, also known as intensity or grades, utilizing the NCI-CTCAE grading scale v5.0 (NCI-CTCAE, 2017). That version will be used for grading AEs, except, as follows:

a. For CRS and infusion reactions for which the ASTCT CRS Consensus Grading (Table 4; Lee, 2019) will be employed
b. For immune effector cell-associated neurotoxicity syndrome, the ASTCT ICANS Consensus Grading for Adults (Table 5, Lee, 2019) will be employed.

Note: some grades are not available for certain AEs (eg, Headache can only be Grade 1, 2, or 3; and Sepsis can only be Grade 3, 4, or 5).

AEs **not contained** within CTCAE Version 5.0 will be rated on a 5-point scale as described below (Table 18).

Table 18: Severity Grading Scale

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

ADL = activities of daily living.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
Note: A semi-colon indicates "or" within the description of the grade.

Any change in severity of the AE over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria under Section 10.2. An AE of severe intensity may not be considered serious.

10.2.3.2. Causality

The Investigator will assess the causality/relationship between the study treatment and the AE.

The Investigator determines if there is a "reasonable possibility" that the study treatment caused the event (causality would be considered as related). Reasonable possibility is defined as evidence to suggest a causal relationship between the study treatment and AE. One of the following categories should be selected based on good medical and scientific judgment, considering the definitions in Table 19 and all contributing factors.

Table 19: Causality Assessment Categories

*For the purposes of regulatory reporting, if the Investigator chooses one of the following categories, the AE will be identified as "**related by the Investigator.**"*	
Related	A clinical event, including laboratory test abnormality that occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. Biological plausibility or causality mechanism should be considered when assessing events as related. The response to withdrawal of the treatment (dechallenge [a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge [b] procedure if necessary.
Probably Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge [b] information is not required to fulfill this definition.
Possibly Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on treatment withdrawal may be lacking or unclear.
*If the Investigator chooses one of the following below, the AE will be identified as "**not related by the Investigator.**"*	
Unlikely Related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.
Not Related	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

[a] Dechallenge is when a drug suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, this is termed a positive dechallenge. If the symptoms continue despite withdrawal of the drug, this is termed a negative dechallenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

[b] Rechallenge is when a drug suspected of causing an AE in a specific subject in the past is readministered to that subject. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

10.2.3.3. Action Taken

Action taken with the study drug will be defined as one of the following:

- Dose not changed
- Dose reduced
- Drug interrupted
- Drug withdrawn
- Not applicable

10.2.3.4. Outcome

Outcome will be defined as one of the following:

- Not recovered or not resolved
- Recovered or resolved
- Recovered or resolved with sequelae
- Recovering or resolving
- Fatal
- Unknown

10.3. Evaluation of Subjects Who Experience an Adverse Event during the Study

Subjects who experience an AE during the study will be evaluated to determine the outcome of the event. The clinical course of the event will be followed, according to the accepted standards of medical practice, until one of the following conditions is met:

1. Resolution
2. The event has stabilized
3. The subject withdrew consent or was lost to follow-up

For all AEs, the date and time of onset and resolution must be captured, if known. This is especially important for CRS, CRS-like events, neurotoxicity, or any infusion reactions. Onset and resolution times must be captured for these events. Failure to record these data will result in a deviation. All SAEs that are continuing at the completion of the study must be followed to determine outcome, as defined previously, to adequately evaluate the subject's safety.

In addition, any procedures performed and medications given to treat the AE(s) (details to include medication name, start date and time, stop date and time, dose, route, frequency, and reason for administration) should be recorded.

10.4. Pregnancy and Breastfeeding

10.4.1. Reporting of Pregnancy

The teratogenic potential of plamotamab is unknown. During the study, and for 6 months (male subjects) and 8 months (female subjects) after the last dose of plamotamab, lenalidomide, and/or tafasitamab, all women of childbearing potential or any partner of a male subject must be instructed to contact the Investigator immediately if pregnancy is suspected. Pregnancy in a subject or partner of a male subject who is receiving treatment should be reported following procedures for an SAE

(although it will not be labeled as an SAE). The pregnancy event will be recorded on the pregnancy report form. Elective abortions without complications should not be reported as AEs.

If pregnancy is suspected in a subject prior to study treatment administration, the study treatment must be withheld until the β-hCG test result is available. If pregnancy is confirmed, the subject must not receive study treatment and must be withdrawn from the study. If pregnancy is suspected while the subject is receiving study treatment, the study treatment must be immediately withheld until the result of a β-hCG test result is available. If pregnancy is confirmed, the subject will be permanently discontinued from the study in an appropriate manner.

The Investigator must immediately notify the Sponsor of any pregnancy that occurs in subjects during study treatment exposure and for at least 8 months after drug administration for female subjects and 6 months for sexual partners of male subjects. Protocol-required procedures for study discontinuation must be performed unless contraindicated by pregnancy (eg, X-ray studies). Other appropriate follow-up procedures should be considered, if indicated. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented to the Sponsor even if the subject was discontinued from the study. The follow-up period will be deemed to have ended when the health status of the child has been determined on its birth.

All outcomes of pregnancy must be reported by the Investigator to the Sponsor and ICON PLC on the pregnancy outcome report form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion and approximately 30 calendar days postpartum.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours of awareness in accordance with the procedure for reporting SAEs. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Infants should be monitored for a minimum of 8 weeks after birth.

10.4.2. Breastfeeding

It is unknown whether plamotamab is secreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breastfeeding or to discontinue plamotamab, taking into account the benefit of breastfeeding for the child and the benefit of plamotamab therapy for the woman.

10.4.3. Embryo-Fetal Toxicity from Lenalidomide WARNINGS AND PRECAUTIONS Section

Lenalidomide is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes life-threatening human birth defects or embryo-fetal death (see Revlimid® PI, 2021, "Use in Specific Populations" [8.1]). An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy.

Women of Childbearing Potential:

Women of reproductive potential must avoid pregnancy for at least 4 weeks before beginning lenalidomide therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide therapy. Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10 days and the second test within 24 hours prior to prescribing lenalidomide therapy. Thereafter, tests should occur weekly during the first month, then monthly thereafter in females with regular menstrual cycles, or every 2 weeks in females with irregular menstrual cycles.

Males:

Lenalidomide is present in the semen of subjects receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide and for up to 4 weeks after discontinuing lenalidomide, even if they have undergone a successful vasectomy. Male subjects taking lenalidomide must not donate sperm.

Blood Donation:

Subjects must not donate blood during treatment with lenalidomide and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female subject whose fetus must not be exposed to lenalidomide.

Pregnancy Exposure Registry:

There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to lenalidomide during pregnancy as well as female partners of male subjects who are exposed to lenalidomide. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to lenalidomide to the Sponsor.

Risk Summary:

Based on the mechanism of action (see Revlimid® PI, 2021, "Clinical Pharmacology" [12.1]) and findings from animal studies (see Data]), lenalidomide can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy (see Revlimid® PI, 2021 for Boxed Warning, "Contraindications" [4.1], and "Use in Specific Populations" [8.0]). Lenalidomide is a thalidomide analogue. Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants. Lenalidomide caused thalidomide-type limb defects in monkey offspring. Lenalidomide crossed the placenta after administration to pregnant rabbits and pregnant rats [see Data]. If this drug is used during pregnancy, or if the subject becomes pregnant while

taking this drug, the subject should be apprised of the potential risk to a fetus. If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer subject to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to lenalidomide to the Sponsor. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk in the US general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Please also refer to lenalidomide prescribing information for pregnancy prevention and other reproductive, issue-related questions (Revlimid® PI, 2021).

11. STATISTICS

11.1. General

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final clinical study report.

For descriptive summaries, continuous variables will be summarized with N (ie, sample size), mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum (min), and maximum (max), and discrete variables will be summarized with frequencies and percentages. Summary results will be displayed by treatment group.

11.2. Primary Objective Estimand

The primary objective of this study is to determine the safety and efficacy of the combination of plamotamab, tafasitamab, and lenalidomide compared to tafasitamab and lenalidomide in adult subjects with relapsed or refractory diffuse large B-cell lymphoma using Lugano 2014 criteria (Cheson, 2014). The attributes for the estimand for the primary objective are outlined in Table 20.

Table 20: Primary Objective Estimand

Primary Estimand				
Population	**Variable**	**Summary Measure**	**Treatment**	**Potential Intercurrent Events**
Intent-to-treat: all randomized subjects in Part 2	Blinded Independent Review Committee assessment of PFS, defined as the time from randomization to first documentation of progressive disease or death, whichever comes first.	Hazard ratio based on Cox regression model stratified by IPI risk score at baseline, number of lines of prior therapy, and primary refractory. KM estimates for median, Q1 and Q3. Stratified log-rank test for treatment effect.	Plamotamab, tafasitamab, and lenalidomide versus tafasitamab, and lenalidomide	Discontinuation of treatment(s), start of a new anti-cancer therapy, including transplant and missing two or more tumor assessments. Treatment policy estimand will apply for intercurrent events.

IPI = international prognostic index; PFS = progression-free survival.

11.3. Sample Size and Power

11.3.1. Progression-Free Survival

PFS as assessed by the BIRC is the primary endpoint for Part 2 of this study. For determination of the sample size, it is assumed that triple combination treatment could improve the median PFS from 12 months (under treatment with tafasitamab + lenalidomide (Duell, 2021) to 23.5 months under the triple combination treatment (plamotamab + tafasitamab + lenalidomide), corresponding to a hazard ratio (HR) of 0.51 with all randomized subjects (it is estimated that 90% of subjects will be central pathologically confirmed as DLBCL).

The log rank test has 90% power with the sample size of 200 (93 events) to preserve the type-I error of 0.025 (one-sided). A loss to follow-up rate of 1.5%/month was assumed for sample size calculations.

Subjects will be randomized 1:1, stratified by IPI risk score at baseline (3 to 5 versus 0 to 2), number of lines of prior therapy (1 versus ≥ 2), and primary refractory (yes versus no). A maximum of 36 primary refractory subjects may be enrolled into the sample size of 200.

Enrollment of 200 subjects is estimated to require 27 months with minimum follow-up time of 6 months. The primary efficacy analysis will occur when 93 PFS events per independent review have been observed. Efficacy boundaries and estimated timing for the analysis is displayed in Table 21.

Table 21: Efficacy Boundaries and Properties for Progression-Free Survival Analyses

Analysis	**Value**	**Efficacy**
Final	**Z**	**1.9600**
N: 200	p (1-sided)	0.0250
Events: 93	**HR at bound**	**0.6659**
Month: 33	P(Cross) if HR = 1	0.0250
	P(Cross) if HR = 0.51	0.9000

p (1-sided) is the nominal α for testing.
HR at bound is the approximate HR required to reach an efficacy bound
P(Cross if HR = 1) is the probability of crossing a bound under the null hypothesis
P(Cross if HR = 0.5) is the probability of crossing a bound under the alternative hypothesis
HR = hazard ratio.

An interim analysis for OS at the time of final PFS analysis will be implemented using the group sequential design in addition to the final OS analysis. Table 22 provides the timing of PFS and OS analysis.

Table 22: Summary of Interim and Final Analyses Strategy

Analyses	**Key Endpoints**	**Timing**	**Estimated Time after First Subject Randomized**	**Primary Purpose of Analysis**
PFS Final OS IA1	PFS ORR OS TTF	93 PFS event and approx. 50 OS events (65% of expected total OS events) have been observed	Approx. 33 months	• Final analyses for PFS, ORR, and TTF • Interim OS analyses
Final OS Analysis	OS	When approx. 76 OS events have been observed	Approx. 51 months	• Final OS analyses

ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure.

11.3.2. Overall Survival

Overall survival will be assessed in the randomized population (Part 2). The one-sided α level for testing OS is at 0.025. It is assumed that the median OS for the Part 2 Arm B is 34 months and that Part 2 Arm A will have 40% improvement from Arm B (ie, median OS = 56.6 months, HR = 0.60). In addition, assuming completion of enrollment in 27 months, a minimum follow-up time of 24 months, and an OS censoring rate (dropout rate) of approximately 1% per month, the study will result a statistical significance with 60% of power. Once 65% of the information (death events) is

available, an interim analysis for OS is planned. Superiority analyses will be performed during the interim and final analyses. Table 23 provides more details.

Table 23: Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	**Value**	**Efficacy**
IA 1: 65%*	**Z**	**2.5469**
N: 200	p (1-sided)	0.0054
Events: 50	**HR at bound**	**0.4833**
Month: 33.8	P(Cross) if HR=1	0.0054
	P(Cross) if HR=0.6	0.2263
Final	**Z**	**1.9896**
N: 200	p (1-sided)	0.0233
Events: 76	**HR at bound**	**0.6326**
Month: 51	P(Cross) if HR = 1	0.0250
	P(Cross) if HR = 0.6	0.6000

*Expected percentage of events with respect to the number of events expected at the final analysis.
p (1-sided) is the nominal α for testing.
HR at bound is the approximate HR required to reach an efficacy bound.
P(Cross if HR = 1) is the probability of crossing a bound under the null hypothesis
P(Cross if HR = 0.6) is the probability of crossing a bound under the alternative hypothesis
HR = hazard ratio; IA = interim analysis
Efficacy bounds derived using a Lan-DeMets O'brien-Fleming approximation spending function.

11.3.3. Objective Response Rate

The one-sided α level for testing ORR is at 0.025. It is assumed the ORR for Part 2 Arm B is 60% and ORR for Part 2 Arm A is 78%. 100 subjects per arm will provide 80% power for statistical significance at 0.025.

11.3.4. Statistical Testing Sequence

The following secondary endpoints will be tested sequentially in the following order, if the test for the primary endpoint is positive:

1. ORR by BIRC per Lugano 2014 criteria (Cheson, 2014)
2. OS
3. TTF

Other secondary efficacy endpoints will be assessed, including:

- PFS, as assessed by Investigator
- ORR by Investigator
- DOR among subjects achieving an objective response
- DOR among subjects achieving a CR

11.4. Independent Data Monitoring Committee

A separate charter will describe the membership and operation of the IDMC. In Part 2, accumulating safety data will be reviewed by the IDMC periodically, as detailed in Section 4.9.

11.5. Analysis Sets

The following populations will be used for analysis as defined below:

- **Enrolled Analysis Set**: All subjects who signs the informed consent form, is determined to be eligible, and receives the Day –8 tafasitamab dose
- **Safety Run-in Analysis Set:** All subjects who are enrolled in Part 1 of the study and receive at least 1 dose each of plamotamab, tafasitamab, and lenalidomide
- **Randomized (Intent-to-Treat) Analysis Set**: All subjects who are randomized into Part 2 of the study
- **Randomized Safety Analysis Set**: All subjects who are randomized into Part 2 of the study and receive at least 1 dose of plamotamab, tafasitamab, or lenalidomide
- **Pharmacodynamic Analysis Set (s)**: All subjects who are enrolled in the study, receive at least 1 dose of study therapy, and have at least 1 set of pre- and post-infusion pharmacodynamic data available for analysis — defined independently for Parts 1 and 2.
- **PK Analysis Set (s)**: All subjects who are enrolled in the study, receive at least 1 dose of study therapy, and have at least 1 set of pre- and post-infusion PK data available for analysis — defined independently for Part 1, Arm A, and Arm B.
- **Plamotamab Treated Analysis Set**: All subjects treated with any amount of plamotamab in Part 1 or Part 2.

11.6. Key Subgroups

Key subgroups include:

- IPI risk score at baseline (3 to 5 versus 0 to 2)

- Primary refractory (yes versus no)
- Number of lines of prior therapy (1 versus ≥ 2)

11.7. Subject Characteristics and Disposition

The SAP will define analysis parameters for the study and takes precedence over this protocol section.

Demographic and baseline characteristics will be summarized, as will disease-related characteristics (including any available genetic data), prior anti-cancer therapies, and relevant supportive care therapies.

A summary of subject disposition will include the following, by Part and by Arm:

- Number of subjects enrolled
- Number of subjects who received each study treatment
- Number of subjects who terminated treatment earlier and reason for early discontinuation of treatment
- Number of subjects who complete the study follow-up period
- Number of subjects who terminated study earlier and reasons for early study terminations

11.8. Safety Analysis

Safety Analysis will be performed with Safety Analysis Set. Safety variables will include AEs/SAEs, vital signs, PE findings, ECGs, laboratory values, medical history, and concomitant medications, which will be summarized by Part and by Arm.

The extent of exposure to plamotamab and tafasitamab will be summarized based on the number of infusions administered and the number of treatment cycles completed, as well as the total dose received. Lenalidomide exposure will be summarized similarly, based on number of doses taken.

Additional summaries of drug exposure will be provided based on the PK parameters described in Section 11.10.

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). The verbatim term recorded by the Investigator will be mapped to System Organ Class (SOC) and Preferred Term using MedDRA.

TEAEs are defined as events with onset dates on or after the start of study treatment or events that are present before the first infusion of study treatment and subsequently worsen in severity.

AE-related endpoints include:

- Treatment-emergent AEs
- Treatment-emergent SAEs
- Adverse reactions
- Serious adverse reactions
- Treatment-emergent AEs by severity, as defined by NCI-CTCAE Version 5.0
- Treatment-emergent AEs resulting in the permanent discontinuation of plamotamab

All AE-related endpoints will be summarized by SOC and preferred term. At each level of summation, subjects will be counted once, under the greatest severity and strongest study-drug relationship.

The hematology, chemistry, and other laboratory values and change from baseline values will be summarized descriptively for each scheduled assessment time point and grouped by dosing cohort. The baseline value for each laboratory value is defined as the last assessment performed on or prior to the date of first dose of study treatment. The frequencies of Grade 3 and 4 hematologic AEs (including neutropenia, thrombocytopenia, and anemia) will be reported. The toxicity grades for laboratory tests will be based on NCI-CTCAE Version 5.0 (NCI-CTCAE, 2017) criteria. The use of blood transfusions (platelets, RBCs) and/or growth factor support will be reported. Similar analyses will be done for chemistry tests (including liver and renal function tests). Subject listings of all laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified in the subject listings and will include flags for high and low values.

Vital sign results (blood pressure, heart rate, respirations, temperature, and blood oxygen saturation by continuous pulse oximetry) will be summarized descriptively for each scheduled time point. The baseline value for each vital sign measurement is defined as the last assessment performed most recently prior to the first dose of study treatment, and any change from these baseline values will be reviewed. The change of vital signs values from preinfusion will be summarized for each postinfusion point. Preinfusion assessments are defined as last vital assessment prior to the same infusion. Subject listings of all vital data collected during the study will be presented.

ECGs values and change from baseline values will be summarized descriptively for each scheduled time point. Subject listings of all ECG data collected during the study will be presented.

Additional analysis will be performed for AEs of CRS. These will include analyses of time to onset, duration, severity, and associations with laboratory cytokine measurements and missed or delayed doses (ie, CRS may be associated with longer intervals between doses). Graphical summaries will illustrate the timing relative to dosing, the severity of CRS events and cytokine levels.

11.9. Efficacy Analysis

The Randomized (intent-to-treat) Analysis Set defined in Section 11.5 will be used for primary and secondary efficacy analyses, unless otherwise noted. Sensitivity analyses will be provided based on

pathologically confirmed DLBCL. Strata might be combined for the analysis if randomization resulted in sparse stratum. The decision to combine strata will be made prior to the database lock.

The primary analysis will be based on PFS as assessed by the BIRC, defined as the time from randomization to first documentation of progressive disease or death, whichever comes first. Subjects who discontinue the study without progression as assessed by BIRC will be censored according to rules specified in the SAP. Kaplan-Meier methodology will be used to summarize the distribution of PFS, presenting median survival together with its 95% confidence intervals and PFS curves for each treatment arm. The primary inferential comparison between treatment groups will use the log-rank test stratified by the randomization stratification factors listing in Section 11.6. The HR for triple combination treatment versus control and its 95% confidence intervals (CI) will be estimated using a Cox proportional hazards model stratified by the same randomization stratification factors. For the secondary endpoint of PFS as assessed by the Investigator, analyses will be similar to the primary analysis. In addition, the SAP will detail a tipping-point sensitivity analysis of potential impacts of informative censoring among subjects who discontinue the study early without progression as assessed by BIRC (ie, not including on-study subjects administratively censored at the time of the analysis).

Analyses of response will be based on the rate of objective response (ORR = CRR + PRR) by BIRC per Lugano 2014 criteria (Cheson, 2014). By-arm comparisons will be made with a stratified Cochran-Mantel-Haenszel test using randomization stratification factors. In addition, response rates and Barnard's exact confidence intervals will be reported both overall and for the categorical Key Subgroups in Section 11.6. The number and percentage of subjects achieving a best overall response of CR (confirmed and unconfirmed), PR (confirmed and unconfirmed), stable disease, progressive disease, not evaluable, and other disease-specific response criteria will be presented.

In addition to BIRC response assessments, Investigator-assessed responses will be reported similarly, and concordance analyses will be detailed in the SAP.

The duration of objective response will be calculated from the time of initial response (PR or better) to the first documentation of relapse (recurrence after CR), progression, or death. The duration of complete response will be calculated from the time of initial response (CR) to the first documentation of relapse (recurrence after CR), progression, or death among subjects achieving a CR.

Time to event analysis of OS, measured relative to randomization, will be performed based on the Kaplan-Meier method. Median survival time and its 95% confidence interval, as well as the 25th and 75th quartiles with their 95% confidence intervals, will be summarized. Subjects who are alive at end of the study will be censored at last known contact date. By-arm comparisons will utilize the same methods as for PFS.

The potential antitumor effects of plamotamab may be evaluated in subgroups of subjects, including the Key Subgroups defined in Section 11.6. The specifications for these and other similar analyses will be described in the SAP, which supersedes any protocol specifications.

11.10. Pharmacokinetic Analysis

Serum concentrations of plamotamab and tafasitamab will be listed, summarized in tabular form by dosing visit (including, mean, median, range, and 25th and 75th percentiles). Details of additional analyses will be provided in a PK analysis plan.

11.11. Immunogenicity Assays

The incidence and titer of anti-plamotamab antibodies and anti-tafasitamab antibodies will be reported by sample collection time point and treatment arm, as applicable.

12. STUDY ADMINISTRATIVE STRUCTURE

12.1. Study Monitoring

The Sponsor or its designee will monitor the study according to GCP guidelines. The Principal Investigator and study center will permit the Sponsor, its representatives, FDA, and other regulatory agencies outside the United States (OUS) direct access to all original source data and documents for study monitoring audits and inspections. All requested information must be entered into the eCRF in the EDC database. The completed eCRF must be promptly reviewed and electronically signed and dated by the Investigator.

During the study, a Xencor monitor and/or designee will have regular contact with the investigational site for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Xencor/ICON
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to ICON and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

The Principal Investigator may be subjected to a field audit by the Sponsor, ICON, FDA, and/or other regulatory (OUS) inspectors in order to validate the participation of subjects in the study and to verify the data reported in the clinical database. The Sponsor should be notified immediately of any audits scheduled by any regulatory authorities. Copies of audit reports from regulatory authorities should be promptly forwarded to the Sponsor.

The Sponsor and Principal Investigator uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data collected and analyzed by the Sponsor will be identified only by an identification number.

ICON will provide the study sites access to the EDC database that will be used to collect the required subject eCRF data for this trial. The eCRF must be supported by the corresponding information in the source document.

12.2. Deviation from Protocol

No deviations from this protocol will be permitted except in a medical emergency. In the case of a medical emergency, the Sponsor's Medical Monitor is notified as soon as possible. Any protocol deviations must be reported to the Ethics Committee or IRB as required by local regulations. The Sponsor or designee will record and compile all protocol deviations.

12.3. Institutional Review Board/Independent Ethics Committee

The Principal Investigator will submit the protocol, protocol amendments, ICF, Investigator's Brochure, and any subject recruitment materials to the IRB/IEC for approval.

It is required that a valid IRB/IEC approves, in writing, the conduct of this clinical study together with the Investigator's ICF prior to study initiation. Until written approval by the IRB/IEC has been received by the Sponsor, no subject may undergo any procedures solely for the purpose of determining eligibility for this study.

The Principal Investigator must provide study progress reports to the IRB/IEC at least annually for all IND studies or more frequently if required by applicable guidelines, regulations, or institutional procedures.

The Principal Investigator must promptly notify the IRB/IEC of any SAEs occurring at the site, as well as any IND safety reports/Expedited Safety Reports, regardless of the reporting site location, if applicable, per local regulations. The Sponsor reserves the right to amend the protocol during the course of the study. It is the Principal Investigator's responsibility to obtain IRB/IEC approval of any protocol amendments and to implement them in a timely manner. Protocol amendments in the form of an administrative letter signed by the Principal Investigator should be submitted to the IRB/IEC for review. All protocol amendments must have IRB/IEC review and approval prior to implementation.

If a protocol amendment substantially alters the study design or increases the potential risk to subjects, the ICF must be revised and submitted to the IRB/IEC for review and approval. The

revised ICF must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment and for all subsequent subjects prior to enrollment.

Documentation of IRB/IEC approval of the protocol, ICF, and other applicable study documents must be provided to the Sponsor or its agent, ICON, before commencement of this study. Copies of all study-related correspondence between the Principal Investigator and IRB/IEC must be maintained in the site regulatory binder.

13. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCPs and all applicable regulatory requirements, the Sponsor or its representatives may conduct a quality assurance audit. See Section 12.1 for more details regarding the audit process.

14. ETHICS

14.1. Ethics Review

Please see Section 12.3 for the Principal Investigator's responsibilities regarding IRB/IEC review.

14.2. Ethical Conduct of the Study

The study will be conducted in compliance with

- the protocol,
- ethical principles of the Declaration of Helsinki (Version 2013) and its amendments,
- the principles of the GCP provided in the Guideline, *E6(R2) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice*
- all applicable national laws and regulations including but not limited to country-specific GCP.

14.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The Principal Investigator is responsible for ensuring that subjects sign and date an appropriately approved ICF prior to enrolling in the study. This must be obtained before conducting any study procedures.

A copy of the signed ICF must be provided to the subject, another copy kept with the study records, and the original kept with the subject's medical records. In addition, the medical record will include documentation of the informed consent process.

The ICF will also indicate that subjects will be informed of important findings of the study by the Principal Investigator and/or staff when data are available and at study completion.

A sample of any ICF to be used in this study that has been approved by the IRB/IEC must be forwarded to the Sponsor or its agent, ICON.

15. DATA HANDLING AND RECORDKEEPING

15.1. Subject Confidentiality

Adequate records must be maintained for the study, including but not limited to subject medical records, eCRFs, laboratory reports, worksheets, nursing notes, signed ICFs, product forms, SAE forms, and information regarding subject discontinuation and reasons for discontinuation. The confidentiality of each record with subject identification is to be guaranteed by the clinical Investigator.

15.2. Inspection of Records

The Sponsor or its designee will monitor the study according to GCP guidelines. The Principal Investigator and study center will permit the Sponsor, its representatives, FDA, and other regulatory agencies direct access to all original source data and documents for study monitoring audits and inspections. All requested information must be entered into the eCRF in the EDC database. The completed eCRF must be promptly reviewed and electronically signed and dated by the Principal Investigator.

The Principal Investigator may be subjected to a field audit by the Sponsor, ICON, and/or other regulatory (OUS) inspectors in order to validate the participation of subjects in the study and to verify the data reported in the clinical database. The Sponsor should be notified immediately of any audits scheduled by any regulatory authorities. Copies of audit reports from regulatory authorities should be promptly forwarded to the Sponsor.

The Sponsor and Principal Investigator uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data collected and analyzed by the Sponsor will be identified only by an identification number.

ICON will provide the study sites access to the EDC database that will be used to collect the required subject eCRF data for this trial. The eCRF must be supported by the corresponding information in the source document.

15.3. Retention of Records

The Principal Investigator shall retain study drug disposition records, copies of CRFs (or electronic files), and all source documentation (such as original ECG tracings, laboratory reports, inpatient, or office subject records) for the maximum period required by the country and Institution in which the study will be conducted or for the period specified by the Sponsor, whichever is longer. The Principal Investigator must contact the Sponsor prior to destroying any records associated with the study. If the Principal Investigator withdraws from the study (due to relocation, retirement, etc.) the records shall be transferred to a mutually agreed upon designee, such as another Principal Investigator or the IRB/IEC. Notice of such transfer will be provided in writing to the Sponsor.

16. PUBLICATION POLICY

By signing the clinical study protocol, the Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without receiving approval from the Sponsor in advance. Authorship criteria for all publications of Xencor-sponsored clinical trials are based on the International Committee of Medical Journal Editors (ICMJE) guideline, "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (ICMJ, 2019). Authorship credit can be granted only to those who make substantial contributions to the publication.

At a minimum, study results will be publisltrials.gov on all primary and secondary outcomes, no later than 1 year after completion of the study (including completion of the study if it has been terminated early).

This protocol and other study documents contain trade secrets and commercial information that is privileged and confidential. Such information is not to be disclosed unless required by laws or regulations. The Principal Investigator agrees to use this information only in conducting this study and is not allowed to use it for other purposes without written consent from the Sponsor. Results obtained from this study are the property of the Sponsor.

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