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STATISTICAL ANALYSIS PLAN

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VERSION

1.1

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

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TABLE OF CONTENTS

1. INTRODUCTION 5
2. STUDY OBJECTIVE(S) AND ENDPOINT(S) 6
2.1. Primary Objectives 6
2.2. Secondary Objectives 6
2.3. Exploratory Objectives 6
2.4. Endpoints 7
2.4.1. Primary Endpoints 7
2.4.2. Secondary Endpoints 7
2.4.3. Exploratory Endpoints 8
3. STUDY DESIGN AND SCHEDULE OF ASSESSMENTS 9
3.1. Study Design 9
3.1.1. Part 1: Single-Arm, Safety Run-In 9
3.1.2. Part 2: Open-Label Randomized 10
3.2. Schedule of Assessments 10
4. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING 11
4.1. Changes in Planned Analyses from the Protocol 11
4.2. Derived and Transformed Data 11
4.2.1. Study Day 11
4.2.2. Missing Data 11
4.2.2.1. Partial/Missing Dates 11
5. STATISTICAL CONSIDERATIONS 12
5.1. Determination of Sample Size 12
5.2. Interim and Final Analyses 12
6. ANALYSIS SETS 14
7. STUDY ANALYSES 15
8. REFERENCES 16
9. IMPUTATION OF PARTIAL AND MISSING DATES 17

List of Abbreviations

AE	adverse event
BMI	body mass index
C_{max}	maximum observed serum concentration
$C_{min[trough]}$	trough concentration
CR	complete response
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ICH	International Conference on Harmonisation
IV	intravenous
MCC	Merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
NCI	US National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD1	programmed cell death 1
PDL1	programmed cell death ligand 1
PFS	progression-free survival
PK/PD	Pharmacokinetics/Pharmacodynamics
PR	partial response
RD	recommended dose
RECIST	Response Evaluation Criteria In Solid Tumors
SAP	statistical analysis plan
SCLC	small cell lung cancer
SRC	Safety Review Committee
TEAE	treatment-emergent AE

1. INTRODUCTION

This statistical analysis plan (SAP) describes the methods to be used for analysis and reporting of clinical data collected throughout the study. It is intended to supplement the study protocol (Version 2.0, 08 March 2022), which contains details regarding the design and conduct of the study. This plan should be read in conjunction with the study protocol and the electronic case report forms (eCRFs).

The study has been terminated early by the sponsor. Only 3 subjects have been enrolled in the study. No efficacy or pharmacokinetic-pharmacodynamic (PK-PD) analyses will be performed. Due to the small sample size, only demographics, baseline characteristics, safety, and efficacy listings will be generated.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. 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.

2.2. 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

2.3. 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

2.4. Endpoints

2.4.1. 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.

2.4.2. 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

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

2.4.3. 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

3. STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

3.1. 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 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.

3.1.1. 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
- Cohort 1B commences enrollment after the 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

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 1: 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.

3.1.2. 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 (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.

3.2. Schedule of Assessments

See study protocol Section 5 Study Assessments.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

All data analysis output will be generated using SAS version 9.4 or later.

4.1. Changes in Planned Analyses from the Protocol

The study has been terminated early by the sponsor. Only 3 subjects have been enrolled in the study. No efficacy or PK-PD analyses will be performed. Due to the small sample size, only listings for demographics, baseline characteristics, safety, and efficacy assessments will be generated.

4.2. Derived and Transformed Data

4.2.1. Study Day

If the date of assessment occurs on or after the first dose date, then study day will be calculated as (date of assessment – date of first dose) + 1. If the date of assessment occurs prior to the first dose date, then study day will be calculated as (date of assessment – date of first dose). There is no study day 0.

4.2.2. Missing Data

Unless otherwise specified, missing data will be treated as missing, ie, no special handling/ missing data imputation will be performed.

4.2.2.1. Partial/Missing Dates

For partial dates, the algorithms for imputation will vary depending upon the parameter; missing or incomplete medications start and stop dates will be imputed to determine whether the medications are taken concomitantly. Eg, missing adverse event (AE) start dates will be imputed to determine whether the adverse events are treatment emergent. In listings, all dates will be listed as recorded. The details of imputation rules can be found in Appendix 1.

5. STATISTICAL CONSIDERATIONS

5.1. Determination of Sample Size

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).

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.

5.2. Interim and Final Analyses

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 2 provides the timing of PFS and OS analysis.

Table 1: Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Subject Randomized	Primary Purpose of Analysis
PFS Final OS IA	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.

6. 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.

7. STUDY ANALYSES

The study has been terminated early by the sponsor. Only 3 subjects have been enrolled in the study. No efficacy or pharmacokinetic-pharmacodynamic (PK-PD) analyses will be performed. Due to the small sample size, only demographics, baseline characteristics, safety, and efficacy listings will be generated.

8. REFERENCES

1. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059–68.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials (E9); 1998 Feb 5.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline. Structure and content of clinical study reports (E3); 1995 Nov 30.

4. National Cancer Institute. Common terminology criteria for adverse events v5.0. NCI, NIH, DHHS; 2017 November 27.

5. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5(6):649-55.

9. IMPUTATION OF PARTIAL AND MISSING DATES

Adverse Event

All AE start dates must be entered on the eCRF as complete dates. In the rare case that all or part of an AE start date is missing, but an AE end date is present and after the first dose date, then the AE start date will be imputed as follows for the purpose of determining treatment emergent flag only:

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
Missing	Missing	Missing	Set date to first dose date
year = year of first dose	Missing	Missing/Non-missing	Set month and day to those of first dose
year ≠ year of first dose	Missing	Missing/Non-missing	Set month and day to January 1
year = year of first dose	Non-missing	Missing	Set day to the day of first dose
year ≠ year of first dose	Non-missing	Missing	Set day to first day of onset month

If AE resolution date is present and prior to first dose date, then there is no need to impute incomplete AE start date, as the AE is not treatment emergent, and the event should be in the medical history.

Concomitant Medications

- If year and month are present and day is missing, then set day to first day of the month for start date and set day to last day of the month for end date.
- If year and day are present and month is missing, then set month to January for start date and set month to December for end date.
- If year is present and month and day are missing, then set month and day to January 1st for start date and set month and day to December 31st for end date.
- Completely missing dates will not be imputed.
- If start date is completely missing and end date is on or after the first dose, then the medication will be classified as concomitant; if the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are completely missing will be classified as concomitant.