NCT04628494

Statistical Analysis Plan

GCT3013-05

A Randomized, Open-Label, Phase 3 Trial of Epcoritamab vs Investigator's Choice Chemotherapy in Relapsed/Refractory Diffuse Large B-cell Lymphoma

Primary Compound Number:	Epcoritamab (GEN3013; DuoBody®-CD3xCD20)
Trial Phase (if applicable)	3
Date:	Sep 2025, Version 6.0

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for Trial GCT3013-05 is based on the protocol amendment 6, version 8.0.

SAP Version	Approval Date	Change	Rationale
1/2	Apr 2021	Minor format update	
3	Jan 2023	Implementation of Lugano criteria	Updated to make the response criteria consistent across all EPCORITAMAB studies, i.e., considering CR/PR following PD.
		Modification of censoring rules	Updated the PFS/DOR event/censoring rules according to FDA comments: added censoring for subsequent anti-cancer therapies "prior to PD or death".
		Changes to Efficacy subgroup analyses	Subgroup variables updated based on development priorities and regulatory requests.
		Modification of PRO analyses	Simplify CSR outputs by moving TAS-Q analyses to a separate study report.
		Include subgroups AE summaries	Updated to add safety summary tables by subgroup.
		Update analysis for adverse events of special interest and other safety topics	Updated Table 9, with more safety topics added, based on recent submission experiences.
4	Jan 2024	Modification of censoring rules of PFS	Updated the PFS/DOR event/censoring rules according to FDA comments: added censoring of 2 or more consecutive missed scans prior to PD or death.
		CCI [redacted]	[redacted]
5	July 2024	After consulting with health authorities, the targeted number of OS events at final analysis is increased from ~300 events to ~ 330 events	To mitigate potential impact of confounding factors (such as COVID-19) and help restore the power for the OS analysis
6	Sep 2025	Added OS non-detrimental criteria; and OS exploratory analyses (censoring COVID-19 death, Rank preserved structure failure time model, and inverse	Updated to add prespecified OS non-detrimental criteria if OS primary hypothesis is not rejected. And sensitivity analyses to address cofounding factors such as COVID-

		probability censoring weighting for effective subsequent therapies)	19 related death and subsequent anti-cancer therapies.
		Updated exploratory analyses for OS and PFS by IRC	Multivariate cox regression adjusting for prognostic factors for OS and PFS by IRC; and the same sensitivity analyses will be performed for the PFS by IRC per Lugano criteria. IPCW method will be applied to COVID-19 deaths.

Abbreviations

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (class)
B-NHL	B-cell non-Hodgkin lymphoma
BR	bendamustine and rituximab
BSA	Body Surface Area
CAR-T	chimeric antigen receptor T-cell
CI	confidence interval
Cmax	maximum serum concentration
CR	complete response
CRF	case report form
CRR	complete response rate
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLS	clinical tumor lysis syndrome
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
DNA	deoxynucleic acid
DOR	duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
FDG	Fluorodeoxyglucose
FL	follicular lymphoma
GemOx	gemcitabine and oxaliplatin
HDT	high-dose therapy
HGBCL	high-grade B-cell lymphoma
IAS	Immunogenicity Analysis Set
IC	Investigator's choice
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICF	informed consent form
IDMC	independent data monitoring committee
IMP	investigational medicinal product
IPI	International Prognostic Index
IR	indeterminate response
IRC	independent review committee
ITT	Intent-to-treat set
IV	intravenous(ly)
LDH	lactate dehydrogenase
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria

mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PAS	Pharmacokinetic Analysis Set
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic/pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PT	preferred term
RoW	Rest of the world (not US or Western EU)
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
SAE	serious adverse event
SAF	Safety analysis set
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCT	stem cell transplant
SD	stable disease
SOC	system organ class/standard of care, depending on context
SPM	second primary malignancy
SSC	Sponsor Safety Committee
TEAE	treatment-emergent adverse event
TTNT	time to next anti-lymphoma therapy
TTR	time to response

1 INTRODUCTION

This clinical study report statistical analysis plan (CSR SAP) contains definitions of analysis sets, derived variables, and statistical methods for the planned analyses as specified in Trial GCT3013-05 protocol amendment 6 version 8.0, to be reported in the Clinical Study Report.

1.1 Objectives and Endpoints

Objectives and related endpoints are described in the following Table.

Table 1 Objectives and Endpoints

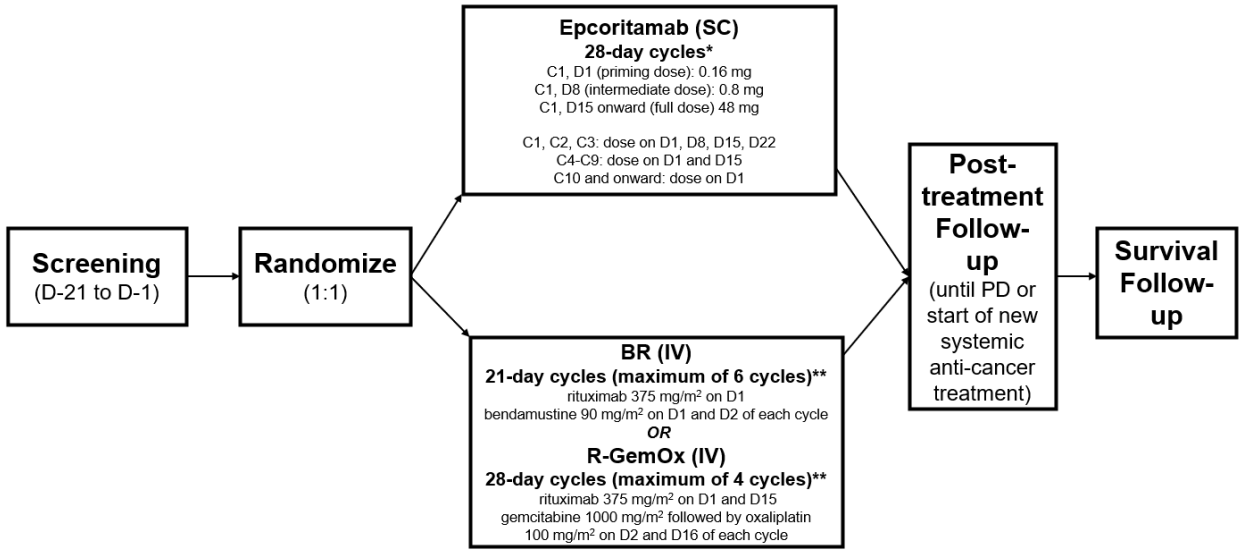
OBJECTIVES	ENDPOINTS
Primary	
• Compare the clinical efficacy of epcoritamab to SOC (R-GemOx or BR)	• OS
Secondary	
• Compare other measures of epcoritamab efficacy to SOC	• PFS determined by Lugano criteria per IRC assessment and investigator assessment • ORR determined by Lugano criteria per IRC assessment and investigator assessment • CR rate, determined by Lugano criteria per IRC assessment and investigator assessment • DOR determined by Lugano criteria per IRC assessment and investigator assessment • TTR determined by Lugano criteria per IRC assessment and investigator assessment • Rate and duration of MRD negative status • PFS determined by LYRIC per IRC assessment • ORR determined by LYRIC per IRC assessment • CR rate determined by LYRIC per IRC assessment • DOR determined by LYRIC per IRC assessment • TTR determined by LYRIC per IRC assessment • TTNT
• Compare safety and tolerability of epcoritamab to SOC	• Incidence and severity of AEs • Incidence and severity of changes in laboratory values • Incidence of dose interruptions and delays
• Evaluate immunogenicity	• Anti-epcoritamab antibody response
• To compare PROs related to lymphoma symptoms between epcoritamab and SOC	• Changes in lymphoma symptoms as measured by the FACT-Lym
Exploratory	
• Evaluate pharmacodynamic markers linked to efficacy and mechanism of action of epcoritamab	• Pharmacodynamic markers in blood samples and within tumor (on-treatment biopsy)
• Assess potential biomarkers predictive of clinical response to epcoritamab	• Circulating tumor DNA • DNA mutation status and gene profile

• To assess impact of lymphoma symptoms and its treatment on health status	• Changes in EQ-5D-3L for health states of interest

AE=adverse event; BR=bendamustine and rituximab; CR=complete response; DOR=duration of response; FACT-Lym=Functional Assessment of Cancer Therapy - Lymphoma; IRC=independent review committee; LYRIC=Lymphoma Response to Immunomodulatory Therapy Criteria; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; R-GemOx=rituximab, gemcitabine, and oxaliplatin; SOC=standard of care; TTNT=time to next anti-lymphoma therapy; TTR=time to response.

1.2 Trial Design

This is a Phase 3, open-label, randomized, global trial of epcoritamab versus SOC (ie, pre-specified investigator's choice of R-GemOx or BR) in 480 subjects aged 18 years or older with R/R (D)LBCL (including DLBCL de novo or transformed, HGBCL with MYC and BCL2 and/or BCL6 rearrangements, FL grade 3B or T-cell/histiocyte-rich large B-cell lymphoma) who failed a previous ASCT or are ineligible for ASCT at screening. The trial will consist of screening (up to 21 days prior to Cycle 1 Day 1), treatment (Cycle 1 Day 1 until treatment discontinuation), Safety Follow-up (after treatment discontinuation until 60 days after last dose), Post-treatment Follow-up (until disease progression or start of new systemic anti-cancer therapy), and survival follow-up (refer to protocol for more information). A diagram of the overall trial design is provided in the following figure.



C=cycle; D=Day; IV=intravenous; PD=progressive disease; SC=subcutaneous
***Until one or more of the discontinuation criteria in Section 8.1 are met**
****Until completion of the maximum cycles or one or more of the discontinuation criteria in Section 8.1 are met**

Subjects will be randomized 1:1 to receive either epcoritamab (n=240) or investigator's choice of R-GemOx or BR (n=240). Prior to randomization, the investigator must select and document the intended choice of chemotherapy (which the subject will receive if randomized to the investigator's choice arm); no change in chemotherapy is permitted for a subject during the treatment phase of the trial. In addition, an enrollment cap will be implemented in the SOC arm

so that at most 50% subjects (N=120) will receive BR. There will also be a cap of approximately 120 subjects (approximately 25% of total enrolment) on the number of second-line subjects (i.e., those with only 1 prior line of therapy) who may be enrolled. Randomization will be stratified by number of prior lines of therapy (1 vs >1), ECOG PS (0-1 vs 2), prior ASCT (yes vs no), and prior CAR-T (yes vs no).

Subjects randomized to receive epcoritamab will be administered epcoritamab as an SC injection in 4-week cycles (i.e., 28 days) as below until one or more of the discontinuation criteria described in protocol Section 8.1 are met:

- Epcoritamab: 0.16 mg SC on Day 1 (priming dose), 0.8 mg SC on Day 8 (intermediate dose), 48 mg (full dose) SC on Days 15 and 22 of Cycle 1; 48 mg SC on Days 1, 8, 15, 22 of Cycles 2 and 3; 48 mg SC on Days 1 and 15 of Cycles 4 through 9; and 48 mg SC on Day 1 of Cycle 10 and onward.

Subjects randomized to SOC will be administered 1 of the 2 chemotherapy options below until completion of the maximum cycles or one or more of the discontinuation criteria in protocol Section 8.1 are met:

- BR: rituximab 375 mg/m^2 IV on Day 1 and bendamustine 90 mg/m^2 IV on Days 1 and 2 of each 21-day cycle for up to 6 cycles
- R-GemOx: rituximab 375 mg/m^2 IV on Days 1 and 15 and gemcitabine 1000 mg/m^2 IV followed by oxaliplatin 100 mg/m^2 IV on Days 2 and 16 of each 28-day cycle for up to 4 cycles. Rituximab, gemcitabine and oxaliplatin may be administered on the same day (Days 1 and 15) if this is standard procedure at site.

Trial assessments will be performed as detailed in the Visit Assessment Schedules in protocol Section 1.

The primary analysis will take place when approximately 330 deaths have accumulated. An independent data monitoring committee (IDMC) will be established for this study to review cumulative safety data after 40 subjects (approximately 20 in the epcoritamab arm) have been treated for at least 1 cycle, and approximately every 4 months thereafter during the trial, according to the IDMC Charter.

1.3 Randomization and Blinding

This is an open-label trial; investigator and trial subjects will therefore not be blinded to treatment arm. Please refer to the GCT3013-05 blinding plan for information about sponsor and external vendor blinding rules.

Eligible subjects will be randomized 1:1 to either epcoritamab or investigator's choice chemotherapy (IC).

Blocked randomization will be stratified by number of prior lines of therapy (1 vs >1), ECOG PS (0-1 vs 2), prior ASCT (yes vs no), and prior CAR-T (yes vs no).

2 STATISTICAL HYPOTHESES

The primary objective of this study is to evaluate if epcoritamab will prolong OS compared to IC in subjects with R/R DLBCL (and FL grade 3B) who failed a previous ASCT or are ineligible for ASCT at screening (see Protocol).

The primary null hypothesis is: there is no difference with respect to OS between the two treatment groups.

The secondary null hypotheses are as follows:

1) There is no difference with respect to PFS between the two treatment groups.
2) There is no difference with respect to ORR between the two treatment groups.
3) There is no difference with respect to CRR between the two treatment groups.
4) There is no difference with respect to TTNT between the two treatment groups.
5) There is no difference with respect to MRD negativity rate between the two treatment groups.

Note: primary/secondary endpoints to be tested will be based on tumor assessment by Lugano per IRC (if applicable).

In the case of failure to reject the OS null hypothesis, the following conditions of no OS detrimental effect of epcoritamab compared to IC will be checked:

- CCI [redacted]
- CCI [redacted]

Both conditions need to be met for claiming no OS detrimental effect.

2.1 Multiplicity Adjustments

To control the overall type I error rate for the primary endpoint and secondary endpoints, one-sided alpha of 0.025 will be allocated to the primary hypothesis of OS and pass on to secondary endpoints sequentially if OS null hypothesis is rejected.

Secondary endpoints will be tested in fixed sequence of PFS, ORR, CR rate, time to next anti-lymphoma therapy (TTNT), and minimal residual disease (MRD), with one-sided alpha of 0.025, if OS result and prior endpoints results are statistically significant.

3 SAMPLE SIZE DETERMINATION

Based on the published data, the median OS for the SOC arm is assumed to be approximately 10 months. Assuming epcoritamab can reduce the risk of death by 30%, i.e., assuming the hazard

ratio (epcoritamab vs. IC) of 0.7, a total of 330 death events will provide ~90% power to detect this hazard ratio with a log-rank test (with one-sided alpha of 0.025).

With a 15-month accrual period and an additional 10-months follow-up, the total sample size needed for the study was estimated to be approximately 480 (240 per arm) subjects.

4 ANALYSIS SETS

4.1 Intent-to-treat (ITT) set

The ITT set includes all randomized subjects. For analyses using ITT set, treatment group will be based on the treatment assignment per randomization.

The ITT set will be used to summarize subject information and efficacy unless otherwise specified.

4.2 Safety Analysis set (SAF)

The safety set includes all randomized subjects who have received at least one non-zero dose of any study drug. For analyses using safety set, treatment group will be based on actual treatment received.

The safety set will be used to summarize exposure and safety data, unless otherwise specified.

4.3 Response-evaluable set (RES)

The response-evaluable set is defined as all treated subjects in ITT who have measurable disease at baseline, histology type as outlined in the protocol inclusion criteria, and at least one post-baseline disease evaluation or have died within 60 days of first dose without post-baseline disease assessment. Measurable disease is defined as:

a. An FDG- PET scan demonstrating positive lesion compatible with CT or MRI-defined anatomical tumor sites AND
b. ≥ 1 measurable nodal lesion (long axis > 1.5 cm and short axis > 1.0 cm) and/ or ≥ 1 measurable extra-nodal lesion (long axis > 1.0 cm) on CT scan or MRI.

The response-evaluable set will be used to summarize response-related data according to randomized treatment assignment as a sensitivity analysis.

4.4 Per-Protocol Set (PP)

The per-protocol set is defined as all treated subjects in ITT, excluding subjects with incorrect histology or incorrect transformation, or no DLBCL appropriate prior line of therapy at baseline.

4.5 Pharmacokinetic Analysis Set (PAS)

The PK analysis set is defined as subjects who have received at least one dose of epcoritamab and have at least one PK concentration value available after the start of first dose. The PK-evaluable set will be used to summarize PK data.

4.6 Immunogenicity Analysis Set (IAS)

The immunogenicity analysis set is defined as subjects who have received at least one dose of epcoritamab and have both the baseline and at least one immunogenicity result available after the start of first dose. The immunogenicity-evaluable set will be used to summarize immunogenicity data.

4.7 PRO Analysis Set

The PRO analysis set is defined as subjects in the ITT with a baseline and at least one postbaseline patient-report outcome (PRO) score (i.e., having at least one item completed for a given questionnaire at baseline and at least one post-baseline value). The PRO analysis set will be used to summarize PRO data.

5 STATISTICAL ANALYSES

5.1 General Analysis Definitions

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation (Std Dev), median and range. Categorical variables will be summarized using frequency and percentage. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries. For the calculation of time-to-event and duration-of-event variables, the difference between the start date and the end date plus one will be used.

Unless otherwise stated, wherever analyses are stratified, all randomization stratification factors will be included; partially stratified analyses may be performed if there are <10 subjects in a stratum, with pooling of small strata.

5.1.1 Study Day and Periods

Study Day 1 or Day 1 refers to the reference start date (the first dose of investigational treatment for treated subjects or the randomization date for non-treated subjects).

Study day or relative day for a visit is defined as:

- Visit date - (date of Day 1) +1, if visit date is ≥ date of Day 1
- Visit date - date of Day 1, if visit date < date of Day 1

5.1.2 Visit Windows

Any efficacy analysis that utilizes time to event approach will be based on an exact determination of time from randomization to the date of event/censoring.

For analyses of data by cycle, if data are collected by date (e.g., AE onset), the corresponding study evaluations will be assigned to actual sequential cycles, which are derived from the study treatment administration data.

In this study, the planned cycles lengths are different (BR cycle length equals 21 days while R-GemOx and epcoritamab cycle lengths equal 28 days) and the planned number of treatment cycles also varies (BR given maximum 6 cycles, R-GemOx given maximum 4 cycles while epcoritamab has no maximum). Some subjects will continue in post-treatment follow-up (visits are to be performed on Q4W intervals) while others will skip this follow-up and move directly to the survival follow-up phase. In addition, due to possible dosing delays, assessment performed in the same cycle may not be well aligned in time scale for different subjects. To address these, visit window rules will be applied for data summaries by study week. Table 2 presents a visit window rule that analyze data every 6 weeks.

Table 2 Analysis by Time Windows

Analysis Period	Time Interval (label on output)	Time Interval (Day)*	Target Day*
Baseline	Baseline	<=1	<1
On-treatment	Week 6	2 to 63	42
	Week 12	64 to 105	84
	Week 18	106 to 147	126
	Week 24	148 to 210	168
	Week 36	211 to 294	252
	Week 48	295 to 420	336
	Week 72	421 to 588	504
	Week 96	589 to 756	672
	Week 120	757 to 924	840
	Week 144	925 to 1092	1008
	Week 156+	1093+	

*Relative to first dosing date, or the randomization date for non-treated subjects

5.1.3 Baseline Value

Baseline value is defined as the last observation on or prior to the first dosing or randomization date (for non-treated subjects). A more detailed definition is provided in Appendix 6.2.

5.1.4 Imputation of Partial/Missing Dates

Unless otherwise specified, no data imputation will be applied for missing values.

The following conventions will be used for imputing missing or partial dates, unless specified otherwise.

- If a date is completely missing, it will be considered as missing.
- If only the day of the month is missing, the 15th of the month will be used to impute the missing day
- If both the day and the month are missing, 01JUL will be used to impute the missing information

For analysis and reporting purpose, partial/missing dates in e.g. adverse event onset/end date, concomitant therapies start/end date, disease initial diagnosis date, and start date of subsequent anti-cancer therapy will be imputed. The detailed imputation rules will be specified in separate documents (ADaM specifications and Data Presentation Plan).

Imputed dates are for analysis only. Original dates will be displayed in the relevant listings.

5.1.5 Treatment Group

Unless otherwise specified, for subject information summaries (Section 5.2), treatment group refers to epcoritamab, R-GemOx, BR, IC and total.

For efficacy and PRO summaries (Section 5.3, 5.4, 5.7.5) treatment group refers to epcoritamab and IC; for exposure and safety summary (Section 5.6) treatment group refers to epcoritamab, R-GemOx, BR and IC.

5.1.6 Duration of Study Treatment, Dose Intensity, and Relative Dose Intensity

Duration of study treatment is defined as the time from the date of the first administration of any study medication to the date of the last administration of any study medication.

Actual dose intensity is calculated as cumulative dose received on and after the first administration of full dose divided by corresponding duration of dosing period.

Relative dose intensity is calculated as actual dose intensity divided by planned dose intensity as described in the protocol. For more details, see Section 5.6.1.

5.1.7 Cycle Start and Cycle End

The start date of a cycle is defined as the date of the first dose of any component of the study treatment, and the end date of a cycle is the start date of the next cycle minus 1. For the last cycle, the end date is defined as the end of treatment visit date, or the minimum of last study treatment date plus 60 days or initiation of subsequent systemic anti-cancer therapy, if the end of treatment visit date is not available.

5.1.8 Year and Month

One-year equals to 365.25 days and one-month equals to 30.4375 days.

5.1.9 Relapsed, Refractory and Primary Refractory

Relapsed disease is defined as disease responding to therapy that has recurred ≥6 months after completion of therapy. Refractory disease is defined as the subject experienced disease progression or stable disease as best response OR disease progression (PD) during therapy or within 6 months after therapy completion. Primary refractory means refractory to first line of treatment.

Table 3 Relapsed, Refractory and Primary Refractory to Prior Therapy

BOR	PD time from completion of therapy <6 months	PD time from completion of therapy >=6 months
CR	Refractory	Relapse
PR	Refractory	Relapse
SD	Refractory	
PD	Refractory	
NE	Refractory	Relapse
Unknown	Refractory	Relapse

5.1.10 Treatment Emergent Adverse Event

A treatment emergent adverse event (TEAE) is defined as any AE with an onset date or worsening grade within the window defined by the time on or after administration of the first dose of study drug through 60 days after the last dose of study drug, or, the date prior to start of subsequent systemic anti-cancer therapy, whichever is earlier (treatment emergent period).

A pre-treatment AE is defined as any non-treatment-emergent AE, with onset before administration of first dose and no worsening during the treatment emergent period.

A post-treatment AE (PTAE) is defined as any AE with an onset date > 60 days after last dose of study drug and before start of subsequent systemic anti-cancer therapy, or as any related serious AE with an onset date > 60 days after last dose.

5.1.11 Subgroups

The following pre-specified subgroup analyses are to be performed for the primary efficacy endpoint, major secondary efficacy endpoints (ORR per Lugano criteria based on IRC assessment, CR rate per Lugano criteria based on IRC assessment, PFS per Lugano criteria based on IRC assessment, TTNT and MRD negativity rate) and safety endpoints, as described below if there are at least 10% of subjects in any category of a subgroup.

Table 4 Subgroups Definitions and Planned Analyses

Subgroup	Definition	Analysis Type
Sex	Male, Female	E, S
Age	< 65 years, 65 to <75 years, ≥ 75 years	E, S
Race	White, Asian, Black, Other	E, S
Baseline Weight	(<65 kg, 65 to <85 kg, ≥85 kg)	E, S
Region 1	North America+Western Europe, ROW	E, S
Region 2	Japan+East Asia countries, ROW	E, S
Region 3	Japan, ROW	E, S
ECOG performance score (IRT)	0-1, 2	E
ECOG performance score (CRF) [2]	0-1, 2/0, 1, 2	E
Number of prior lines of therapy (IRT)	1, 2+	E
Number of prior lines of therapy (CRF) [1] [2]	1, 2+	E, S
Prior ASCT (IRT)	Yes, No	E
Prior CAR-T (IRT)	Yes, No	E
DLBCL disease state	De novo, transformed	E
DLBCL Cell of origin	GCB, ABC/non-GCB	E
LBCL disease type [3]	DLBCL NOS(ex DH/TH), HGBCL, Other	E, S
Bulky disease (central)	< 7cm, 7-10 cm , >10 cm	E
IPI score	0-2, 3-5	E
Ann Arbor stage	I/II, III/IV	E
Prior anti-lymphoma therapy status [1]	Primary Refractory, Other	E
Most recent prior anti-CD20 containing therapy [1]	Refractory, Relapsed	E
Refractory to prior CAR-T	Yes, No	E
Baseline Renal Function	Normal, Mild, Moderate, Severe	S
Baseline Hepatic Function	Normal, Mild, Moderate, Severe	S
Choice of Therapy prior to randomization (IRT)	BR, R-GemOx	E

E: Efficacy (OS, PFS, ORR, CRR, TTNT; MRD); S: Safety (TEAE). ROW = Rest of the World

[1] DLBCL appropriate therapy: All systemic therapies given for DLBCL are counted as “DLBCL appropriate”. Systemic therapies given before transformation to DLBCL or given for treatment of Follicular Lymphoma 3B or T-

cell/histiocyte-rich large B-cell lymphoma, are only counted as "DLBCL appropriate" if considered appropriate therapy for DLBCL.
[2] CRF data may be used for # of prior lines of therapy and ECOG subgroup analysis.
[3] LBCL disease type will be based on the FISH results by central lab.

For the efficacy subgroup analyses, forest plot (unstratified) will be produced. Presentations of AEs in subgroups will be provided: Overview of TEAEs, TEAEs by SOC and PT, Serious TEAEs by SOC and PT, and Grade 3 or higher TEAEs by SOC and PT.

Additional subgroup analyses may be performed for designated subgroup factors and certain regions/countries for regulatory purposes.

5.2 Subject Information

5.2.1 Subject Disposition

Subject enrollment will be summarized by region and country.

The following disposition information will be summarized:

- Number of screened subjects
- Number of screen failures and the corresponding reason
- Number of subjects randomized to each treatment group
- Number of subjects randomized to each treatment group by stratification factor
- Number and percentage of subjects who are treated
- Number and percentage of subjects who are not treated and the corresponding reason
- Number and percentage of subjects who discontinue study treatment and the corresponding reason (including Completed treatment per protocol for subjects receiving SOC)
- Number and percentage of subjects who discontinue study and the corresponding reason

A listing of screen failures will be provided, including the eligibility criteria that were not met. A listing of subject disposition will be provided, including the status/reason of treatment discontinuation and study discontinuation for all randomized subjects.

5.2.2 Demographics and Disease Characteristics

All summaries will be presented by treatment group.

The following baseline demographic information will be presented: age (continuous), age categories (< 65 years, 65 to <75 years, ≥ 75 years), gender, race, ethnicity, weight (kg), height (cm), Body Mass Index (kg/m^2), body surface area (m^2), and Region.

The following baseline disease characteristics will be summarized: histology type, disease type, molecular classification, time from initial diagnosis to randomization, Ann-Arbor staging, R-IPI score, proportion of subjects with constitutional symptoms, ECOG performance score, number of

prior line(s) of systemic therapy, prior-ASCT, prior CAR-T, and ADA. Additional parameters may be included based on the subgroup analysis.

5.2.3 Prior Therapies

5.2.3.1 Prior Exposure to Anti-Lymphoma Therapies

The number and percentage of subjects with prior anti-lymphoma therapy related to disease under study, including systemic anti-lymphoma therapy, prior radiotherapy, prior surgery, prior ASCT, and/or prior CAR-T, will be provided. In addition, the reason for ineligibility for HDT-ASCT will be provided.

The number of prior lines of systemic therapy and number of prior lines of anti-CD20 containing therapy will be summarized descriptively. Summary of prior systemic therapy will also be presented by type. In addition, time from end of last line of systemic therapy and time from end of last anti-CD20 containing therapy to randomization date will be summarized descriptively.

All prior systemic therapies will also be summarized by Anatomical Therapeutic Chemical (ATC) class according to World Health Organization (WHO) Drug Dictionary

All prior systemic therapies, radiotherapy and surgery will be listed by subject.

5.2.3.2 Refractory or Relapsed Disease

The number and percentage of subjects with the following types of disease will be tabulated:

- primary refractory (i.e. refractory to first line of therapy)
- refractory to at least two consecutive lines of prior therapy
- refractory to last line of prior therapy
- relapse to first line therapy
- relapse to last line of prior therapy

5.2.4 Prior and Concomitant Medications

Medications will be considered as either prior or concomitant medications. Prior medication is defined as medication that ended prior to the first dose of study drug. Concomitant medication includes medications taken (or ongoing) on or after the first dose of study treatment through 60 days after the last dose of study treatment or initiation of subsequent systemic anti-cancer therapy, whichever occurs first.

Medications will be coded to preferred term and ATC therapeutic class according to WHO Drug dictionary.

The incidence of prior and concomitant medications will be summarized by ATC and preferred drug name. Corticosteroids recorded as being administered as pre-medication or prophylaxis in the CRF will be tabulated and listed separately.

Concomitant medications required for treating CRS and ICANS will be summarized.

The total dose of steroids taken will be presented descriptively.

5.2.5 Medical History

Medical history findings reported by the investigator will be coded using the most recent MedDRA version before database lock and summarized by system organ class and preferred term. The diseases will be classified as follows:

- Previous medical conditions (or surgeries), i.e. conditions that stopped prior to first dose.
- Ongoing (concomitant) medical conditions (or surgeries), i.e. conditions still present at first dose.

The frequency of medical history conditions will be presented after classification into previous and concomitant conditions by system organ class (SOCs) as well as the frequencies of preferred terms (PT) within each SOC.

5.2.6 Protocol Deviations

Protocol deviations will be based on clinical review, e.g. including but not limited to the following: eligibility criteria, treatment compliance (including receiving disallowed concomitant medication and/or incorrect treatment/dose), safety assessment deviation, efficacy assessment deviation, and others which might significantly impact safety/efficacy assessment. Protocol deviations will be closely monitored during the execution of the study and the final set of protocol deviation criteria will be finalized before database lock.

Subjects with protocol deviations will be summarized by types of deviation and listed separately.

5.2.7 Subsequent Anti-Cancer Therapies

Subsequent anti-cancer therapies are defined as any therapy (systemic, radiotherapy, surgery) started after study drug has been permanently discontinued (after randomization for non-treated subjects). Subsequent anti-cancer therapies will be coded to preferred drug name and Anatomical Therapeutic Chemical (ATC) class according to World Health Organization (WHO) Drug dictionary.

The number and percentage of subjects who received any subsequent anti-cancer therapy will be summarized, overall and in the categories systemic therapy, radiotherapy, surgeries. All subsequent anti-cancer therapies will also be presented by therapeutic class (ATC) and preferred drug name.

5.3 Primary Endpoint/Analysis

The primary endpoint of this study is overall survival (OS).

5.3.1 Analyses of OS

5.3.1.1 Definition of Endpoint

OS is defined as the time from the date of randomization to the date of death due to any cause. Subjects who are still alive at the clinical cut-off date for the analysis will be censored at the last date known to be alive.

5.3.1.2 Main Analytical Approach

The number and percentage of subjects with OS event or censoring will be reported. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. Median OS with its 95% CI will be provided. In addition, landmark survival rates, together with the corresponding 95% CI, will be presented for each treatment group. The Kaplan-Meier OS curve will also be plotted by treatment group.

The p-value for testing treatment effect will be based on a stratified log-rank test. The treatment effect (hazard ratio) and its two-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable, and Efron's method of handling ties. Stratification factors include number of prior lines of therapy (1 vs >1), ECOG PS (0-1 vs. 2), prior ASCT (yes vs. no) and prior CAR-T (yes vs. no). In case of insufficient information in any stratum (<10 subjects), a partially stratified approach (neighboring small strata are combined based on prognostic risk score) will be applied, in addition to the fully stratified analysis.

Reason for OS censoring will be summarized. Summary for duration of study follow-up will be provided. The median duration of study follow-up will be estimated using Kaplan-Meier method.

Table 5 provides a description of attributes of the OS estimand.

Table 5 Attributes of the Estimand – Primary Endpoint OS

Estimand Label	Treatment	End - point	Population	Handling of Intercurrent Events	Statistical Summary
Overall Survival	Treatment arm: Epcoritamab Control arm: BR or R-GemOx	Overall Survival	Subjects with R/R DLBCL (and FL grade 3B) who failed a previous ASCT or are ineligible for ASCT at screening	• Discontinuation of study drug will be ignored • Initiation of subsequent anti-cancer therapy (NALT) prior to death will be ignored • Study discontinuation (missing death date): Subjects will be censored at last know alive date • Lost to follow-up (missing death date): Subjects will be censored at last known alive date • Without post-baseline follow-up (missing death date): Subjects will be censored at randomization	• P-value based on stratified log-rank test • Hazard ratio with its 95% CI estimated by stratified Cox regression • Number and percentage of deaths and censors by arm • K-M curve by arm • Median and their 95% CI based on Kaplan-Meier estimates by arm • Survival rates, 95% CI based on Kaplan-Meier estimate at different landmarks by arm

5.3.1.3 Sensitivity Analysis

Sensitivity analysis of OS by using unstratified log-rank test and unstratified Cox's regression model will be performed in a similar manner as described in Section 5.3.2. Also, OS analysis based on the safety set with the main analytical approach will be provided.

Multivariate Cox regression for OS adjusting for prognostic and clinically relevant baseline factors, including number of prior lines of systemic therapy, primary refractory/relapse status, age, region, prior ASCT (IRT), prior CAR-T, IPI score (0-2/3-5), DLBCL disease stage, FISH

status by central lab, etc., will be performed. Additional multivariate Cox regression analyses may be performed.

COVID-19 associated death is defined as death with COVID-19 as cause or COVID-19 AE with fatal outcome. OS analysis that censors COVID-19 associated death (COVID-19 associated death will be treated as OS censoring instead of OS event) will be performed for the ITT population with the main analytical approach if COVID-19 associated death happens in >5% of the ITT subjects. In addition, inverse probability censoring weighting method (IPCW) will be applied to COVID-19 associated deaths with the following covariates (including but not limited) to model the probability of COVID-19 associated death on trial: # of prior lines of lymphoma therapy (IRT), ECOG (IRT), age, region, prior ASCT (IRT), prior CAR-T, IPI score (0-2/3-5), DLBCL disease stage, FISH status by central lab, primary refractory/relapse status, and overall timepoint assessment/BOR assessed by investigator and/or IRC.

To evaluate the impact of effective subsequent therapies (CAR-T or CD3-CD20 bi-specifics mAb containing therapies) on overall survival, analyses using the rank preserved structural failure time (RPSFT) model and the inverse probability censoring weighting method (IPCW) will be conducted. IPCW may choose from the same set of covariates specified above for COVID-19 associated deaths.

To account for potential deviation from the proportional hazard assumption, additional sensitivity analyses of OS may be performed, such as comparison between treatment groups of landmark survival rates at key timepoints such as 9, 12, 18, and 24 months, restricted mean survival time (RMST) comparison, and other appropriate exploratory statistical methods.

5.3.1.4 Supplementary Analyses

Subgroup analyses will be performed using potential prognostic variables listed in Section 5.1.11 to investigate the consistency and robustness of the primary analysis.

The hazard ratio of Epcoritamab over IC with its 95% CI will be calculated based on an unstratified Cox regression model for each subgroup and be presented in a forest plot.

OS summary and comparison of Epcoritamab vs BR and Epcoritamab vs R-GemOx will be provided, based on ITT and prior choice of IC before randomization (as a subgroup factor), by unstratified log-rank test and unstratified Cox regression model.

5.4 Secondary Endpoints Analysis

Response to study treatment will be evaluated by independent review committee (IRC) and by the investigator based on the Lugano criteria. In the derivation of Lugano based endpoints, date of PD is defined as the earliest date of documented progression after which there is no more PR or CR assessment.

Inferential hypotheses testing for the key secondary endpoints will be performed only after statistical significance is claimed for the primary endpoint.

The fixed sequence approach, which strongly controls the familywise type I error rate, will be implemented to sequentially test the following key endpoints in order at the one-sided 0.025 significance level:

1) PFS based on Lugano criteria per IRC assessment
2) ORR based on Lugano criteria per IRC assessment
3) CRR based on Lugano criteria per IRC assessment
4) Time to next anti-lymphoma treatment
5) Overall MRD negative rate

5.4.1 Key Secondary Endpoints

5.4.1.1 PFS Analyses

PFS is defined as the time from randomization to either disease progression or death, whichever occurs first. In the derivation of Lugano based endpoints, date of PD is defined as the earliest date of documented progression after which there is no more PR or CR assessment (to minimize the impact of pseudo-progression). The primary PFS analysis will be based on Lugano criteria per IRC assessment.

Subjects who withdrew consent from the study before disease progression will be censored at the last evaluable disease assessment before withdrawal of consent to study. Subjects who are lost to follow-up will be censored at the last evaluable disease assessment before subjects are lost to follow-up. Subjects who have not progressed and are still alive at the cutoff date for analysis will be censored at the last disease assessment. Subjects without any post-baseline disease assessment will be censored at randomization.

Table 6 provides a description of attributes of the (primary) PFS estimand.

Table 6 Attributes of the Estimand – Secondary Endpoint PFS

Estimand Label	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Progression Free Survival (by Lugano criteria per IRC assessment)	Treatment arm: Epcoritamab Control arm: BR or R-GemOx	PFS	Subjects with R/R DLBCL (and FL grade 3B) who failed a previous ASCT or are ineligible for ASCT at screening	Treatment Policy Strategy for treatment discontinuation ○ Discontinuation of study drug will be ignored Both treatment policy and hypothetical strategies for subsequent anti-cancer therapy ○ Initiation of subsequent anti-cancer therapy prior to PD or death will be ignored ○ Initiation of subsequent anti-cancer therapy prior to PD or death will be censored	• P-value based on stratified log-rank test • Hazard ratio with its 95% CI estimated by stratified Cox regression • Number and percentage of deaths and censors by arm • K-M curve by arm • Median and their 95% CI based on Kaplan-Meier estimates by arm • Survival rates, 95% CI based on Kaplan-Meier estimate at different landmarks by arm

Table 7 displays the event/censoring rule for PFS that censors subsequent anti-cancer therapies prior to PD or death, and Table 8 displays the event/censoring rule for PFS that doesn't censor subsequent anti-cancer therapies prior to PD or death.

Table 7 PFS Event/Censoring Rule - Censoring Subsequent Anti-cancer Therapy

Situation	**PFS date**	**Outcome**
Incomplete or no baseline tumor assessments and subject has not died	Randomization date	Censored
No post-baseline assessments and the subject has not died	Randomization date	Censored
>=2 consecutive missing tumor assessments	Date of last evaluable tumor assessment before the missing assessments	Censored
No progression or death or subsequent anti-cancer therapy*	Date of last evaluable tumor assessment	Censored
Subsequent anti-cancer therapy* started prior to PD or death	Date of last evaluable tumor assessment before start of subsequent anti-cancer therapy	Censored
Progression	Date of PD scan	Event
Death prior to progression	Date of death	Event
* Anti-cancer therapy: systemic treatment, radiotherapy to target lesion(s), non-palliative radiotherapy to other type of lesion(s), surgery to target lesion(s), all new transplants, and CAR-T.		

5.4.1.1.1 Main Analytical Approach

The main analytical approach for PFS is the same as what is described in Section 5.3.1.2 based on IRC assessments per the Lugano criteria on the ITT set, and with the rules defined in Table 7.

5.4.1.1.2 Sensitivity Analysis

The same sensitivity analyses of PFS (per IRC by Lugano) will be done as described in Section 5.3.1.3 based on the ITT set. Key timepoints for PFS landmark analysis are 3, 6, 9, and 12 months.

In addition, the following sensitivity analyses are planned for PFS.

1) Unstratified and partially stratified (see Section 5.3.1.2) analyses, censoring subsequent anti-cancer therapy (Table 7), based on Lugano criteria per IRC assessment
2) Stratified analysis, not censoring subsequent anti-cancer therapy (Table 8), based on Lugano criteria per IRC assessment
3) Stratified analysis, censoring subsequent anti-cancer therapy (Table 7), based on Lugano criteria per investigator assessment

4) Stratified analysis, censoring subsequent anti-cancer therapy (Table 7), based on Lugano criteria per IRC assessment, with COVID-19 death as PFS censoring instead of event.

Table 8 PFS Event/Censoring Rule - Not Censoring Subsequent Anti-cancer Therapy

Situation	**PFS Date**	**Outcome**
Incomplete or no baseline tumor assessments	Randomization date	Censored
No post-baseline tumor assessment and no death	Randomization date	Censored
>=2 consecutive missing tumor assessments	Date of last evaluable tumor assessment before the missing assessments	Censored
No progression or death	Date of last evaluable tumor assessment	Censored
Progression	Date of progression	Event
Death prior to progression	Date of death	Event

5.4.1.1.3 Supplementary Analyses

1) Stratified analysis, censoring subsequent anti-cancer therapy (Table 7), based on LYRIC per IRC assessment.
2) Subgroup analysis, similar to those described in Section 5.3.1.4.

5.4.1.2 Overall Response Rate (ORR)

5.4.1.2.1 Definition of Endpoint

ORR is defined as the proportion of subjects achieving partial response (PR) or complete response (CR), prior to initiation of subsequent anti-cancer therapy. The primary ORR analysis will be based on Lugano criteria per IRC assessment.

5.4.1.2.2 Main Analytical Approach

The best overall response prior to initiation of subsequent anti-cancer therapy will be derived and summarized for the ITT set. The number and percentage of subjects in the following response categories will be presented by treatment group: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE), and overall response (CR + PR). The 95% exact CI for ORR will be provided.

Stratified exact CMH test will be used to test the difference in ORR between treatment groups. The CMH estimate of odds ratio of achieving response (PR or CR), together with its 95% CI, and p-value for testing treatment difference will be provided. Stratification factors to be used in the analysis include number of prior lines of therapy (1 vs >1), ECOG PS (0-1 vs. 2), prior ASCT (yes vs. no) and prior CAR-T (yes vs. no). In case of insufficient information in any stratum (<10 subjects), a partially stratified approach (neighboring small strata are combined based on prognostic risk score) will be applied.

5.4.1.2.3 Sensitivity Analysis

1) Stratified analysis based on Lugano criteria per investigator assessment in the ITT set
2) Stratified analysis based on Lugano criteria per IRC assessment in the response-evaluable set
3) Stratified analysis based on Lugano criteria per investigator assessment in the response-evaluable set
4) In case of insufficient information in any stratum, a partially stratified analysis may be performed based on Lugano criteria per IRC assessment

In addition, the concordance between IRC- and investigator-assessed response based on Lugano criteria in the ITT set will be evaluated using kappa statistics.

5.4.1.2.4 Supplementary Analyses

1) Stratified analysis, based on LYRIC per IRC assessment, ITT set

2) Subgroup analysis, similar to those described in Section 5.3.1.4, except that odds ratio and its corresponding 95% CI will be presented

5.4.1.3 Complete Response Rate (CRR)

5.4.1.3.1 Definition of Endpoint

CRR is defined as the proportion of subjects achieving CR prior to initiation of subsequent anti-cancer therapy. The primary CRR analysis will be based on Lugano criteria per IRC assessment.

5.4.1.3.2 Main Analytical Approach

The main analytical approach for CRR is generally the same as what is described in Section 5.4.1.2.2.

5.4.1.3.3 Sensitivity Analysis

Refer to Section 5.4.1.2.3.

5.4.1.3.4 Supplementary Analyses

Refer to Section 5.4.1.2.4.

5.4.1.4 TTNT analyses

Time to next anti-lymphoma therapy (TTNT) is defined as the time from randomization to first recorded administration of subsequent anti-lymphoma therapy or death due to progression, whichever occurs earlier.

Death due to disease progression will be considered an event. Death due to other reasons will be censored at the death date. The subsequent anti-lymphoma therapies for TTNT events will in general consist of systemic anti-lymphoma therapy, stem cell transplant (SCT), CAR-T therapy, surgery to target lesions and radiotherapy to target lesion(s) except for palliative radiotherapy of non-target lesion(s). Subjects who initiate subsequent SCT therapy while in complete or partial response will be censored at the date of conditioning or high dose chemotherapy prior to SCT. Subjects alive and without initiation of subsequent anti-lymphoma therapy will be censored at the last known alive date.

TTNT will be derived and analyzed in the ITT population.

5.4.1.4.1 Main Analytical Approach

The main analytical approach for TTNT is generally the same as what is described in Section 5.3.1.2.

5.4.1.4.2 Sensitivity Analysis

An unstratified analysis will be performed as a sensitivity analysis. An additional sensitivity analysis will consider all-cause death as an event.

5.4.1.5 MRD negative rate

5.4.1.5.1 Definition of Endpoint

MRD negativity rate is defined as the proportion of subjects who have at least one negative MRD sample (primary threshold for MRD negative at < 1 mutant molecule per ml (MMPM)) at any on-treatment time point. Any subject in the ITT population not determined to be MRD negative will be scored as MRD positive. MRD positive subjects include those whose tested results are always MRD positive, or indeterminate due to calibration or QC failure, or unevaluated.

Additional analyses may be performed at additional MRD thresholds (e.g. < 0.5 MMPM) and/or by landmark analysis of a molecular response at C3D1 (e.g. ≥ log 2.5 fold decrease of the mean MMPM from C1D1).

5.4.1.5.2 Main Analytical Approach

The exact CMH estimate of odds ratio of achieving MRD negativity status, together with its 95% CI, will be provided. Stratification factors used in the analysis include number of prior lines of therapy (1 vs >1), ECOG PS (0-1 vs. 2), prior ASCT (yes vs. no) and prior CAR-T (yes vs no). The p-value for testing the difference in MRD negativity rate will be based on Fisher's exact test since the number of subjects with MRD negative sample may be small. The corresponding 95% exact CI for MRD negativity rate will be presented.

5.4.1.5.3 Sensitivity Analysis

Refer to Section 5.4.1.2.3.

5.4.2 Supportive Secondary Endpoints

5.4.2.1 Duration of Response (DOR), Duration of Complete Response (DOCR)

5.4.2.1.1 Definition of Endpoint

DOR is defined among responders as the time from date of initial documentation of response (PR or CR) to date of disease progression or death, whichever occurs first. In the derivation of Lugano based endpoints, date of PD is defined as the earliest date of documented progression after which there is no more PR or CR assessment.

DOR will be summarized among all responders, and for CR subjects and PR subjects, respectively.

DOCR is defined among complete responders as the time from date of initial documentation of complete response to date of disease progression or death, whichever occurs first.
The primary DOR and DOCR analysis will be based on Lugano criteria per IRC assessment. The censoring rules for DOR and DOCR follows those in Section 5.4.1.1 for PFS.

5.4.2.1.2 Main Analytical Approach

No formal statistical comparison of DOR and DOCR between the two groups is planned. Otherwise, the main analytical approach for DOR and DOCR is the same as those in Section 5.4.1.1 for PFS.

5.4.2.1.3 Sensitivity Analysis

1) Based on Lugano criteria per investigator assessment
2) Based on LYRIC per IRC assessment
3) Based on Lugano criteria per IRC assessment, with COVID-19 related death censored.

5.4.2.2 Time to Response (TTR), Time to Complete Response (TTCR)

5.4.2.2.1 Definition of Endpoint

TTR is defined among responders as the time from randomization date to date of first documentation of response (PR or CR).

TTCR is defined among complete responders as the time from randomization date to date of first documentation of complete response.

The primary TTR and TTCR analysis will be based on Lugano criteria per IRC assessment.

5.4.2.2.2 Main Analytical Approach

No formal statistical comparison of TTR and TTCR between the two groups is planned. Descriptive summaries are to be provided for TTR and TTCR.

5.4.2.2.3 Sensitivity Analysis

1) Based on Lugano criteria per investigator assessment
2) Based on LYRIC per IRC assessment

5.4.2.3 Duration of MRD Negativity Status

5.4.2.3.1 Main Analytical Approach

The durability of MRD negativity may be examined for each treatment group among MRD negative subjects by the Kaplan-Meier method and the proportion of subjects remaining MRD negative 6- or 12- months after initial MRD negativity.

5.4.2.4 FACT-Lym

The FACT-Lym will also be analyzed as secondary endpoint as specified in the protocol and Section 5.7.5.1 of this analysis plan.

5.5 Tertiary/Exploratory Endpoints Analysis

For details on exploratory analyses of Biomarker and PRO endpoints, please see Section 5.7.

5.6 Safety Analyses

5.6.1 Extent of Exposure

The number and percentage of subjects treated within each cycle will be summarized by treatment group. The number of treatment cycles received for each subject will be summarized by frequency and descriptive statistics.

Duration of study treatment in months will be summarized descriptively.

For subjects treated with epcoritamab, the number of epcoritamab administrations will be summarized with descriptive statistics; the total cumulative dose administered for epcoritamab (mg) will be presented descriptively overall. For subjects treated with BR, the number of rituximab and bendamustine administrations will be summarized with descriptive statistics; the total cumulative dose administered for rituximab (mg) and bendamustine (mg) will be presented descriptively. For subjects treated with R-GemOx, the number of rituximab, gemcitabine, and oxaliplatin administrations will be summarized with descriptive statistics; the total cumulative dose administered for rituximab (mg), gemcitabine (mg), and oxaliplatin (mg) will be presented descriptively.

Actual dose intensity is calculated as the cumulative dose received on and after the first administration of full dose in the case of epcoritamab and first dose in the case of IC divided by the duration of analysis period. The first full epcoritamab dose is defined by the first occurrence of a dose greater than 0.8 mg. For IC the distinction between full dose and other doses does not apply.

The actual dose intensity for epcoritamab (mg/cycle) will be summarized descriptively by Cycle (1-3, 4-9, 10+). The overall dose intensity for rituximab (mg/m^2/cycle), bendamustine (mg/m^2/cycle), gemcitabine (mg/m^2/cycle), and oxaliplatin (mg/m^2/cycle), will be summarized descriptively by arm as applicable.

Relative dose intensity (%) is derived as the actual dose intensity divided by the corresponding planned full dose intensity in the analysis period. The relative dose intensity (%) will be calculated for each study medication and summarized by treatment group using descriptive statistics.

The incidence of epcoritamab modification (delay) and rituximab dose modification (delay, reduction, and interruption) and the corresponding reason will be summarized overall. The incidence of dose modification (delay, reduction, and interruption) for bendamustine, gemcitabine, and oxaliplatin will be presented separately for each medication, together with the reported reason.

5.6.2 Adverse Events

Refer to section 5.1.10 for definition of pre-treatment, treatment-emergent and post-treatment adverse events. All AE verbatim terms reported in the eCRF by investigators will be coded using the latest version of MedDRA coding dictionary and graded according to or guided by NCI-CTCAE version 5.0, except for CRS and ICANS which will be graded according to Lee 2019 criteria and CTLS which will be graded according to Cairo-Bishop criteria.

All TEAEs will be included in the analysis.

Most summaries of AEs will be based on TEAEs, and by treatment group. Unless otherwise specified, when reporting the overall incidence of an AE, a subject is counted only once in the SOC/PT summary even if this SOC/PT was reported more than one time. Pre-treatment and post-treatment adverse events (PTAEs) will be included in listings (marked with flag).

Selected safety analysis will be performed on all AEs (TEAEs + PTAEs), and selected safety analysis will be performed by analysis period.

5.6.2.1 Treatment Emergent Adverse Events

The following summaries of TEAEs will be provided:

- Overview of TEAEs
- Overview of TEAEs by Analysis Period
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and Analysis Period
- TEAEs by SOC, PT and relationship to study treatment
- TEAEs by SOC, PT and Grade
- Most common (at least 10%) TEAEs by SOC and PT
- Most common (at least 10%) TEAEs by PT
- Most common (at least 5%) grade 3 or 4 TEAEs by SOC and PT
- Most common (at least 5%) grade 3 or 4 TEAEs by PT
- Grade 3-4 TEAEs by SOC and PT
- Fatal TEAE by SOC and PT
- Serious TEAEs by SOC and PT
- Serious TEAEs by PT
- Most common (at least 2%) serious TEAEs by SOC and PT
- Serious TEAEs by SOC, PT and relationship to study treatment
- Serious TEAEs by SOC, PT and Grade

- TEAEs leading to dose modifications (delay/reduction/interruption) by SOC, PT and Grade
- TEAEs leading to dose modification (delay/reduction/interruption) by PT, Grade, and analysis period
- TEAEs leading to treatment discontinuation by SOC, PT and Grade
- TEAEs leading to treatment discontinuation by SOC, PT, and analysis period

Presentations of AEs in subgroups will be provided regarding Overview of TEAEs, TEAEs by SOC and PT, Serious TEAEs by SOC and PT, and Grade 3 or higher TEAEs by SOC and PT. The subgroups factors are those defined in Section 5.1.11 (subgroup analysis). Additional subgroup analysis may be performed as needed.

All TEAEs will be listed by subject. Additional listings will be produced for all SAEs, all AEs leading to treatment discontinuation, and fatal AEs.

5.6.2.2 All AEs

The following summaries of All AEs (TEAEs + PTAEs) will be provided:

- Overview of AEs
- Overview of AEs by Analysis Period
- AEs by SOC and PT
- AEs by SOC, PT, and Analysis Period
- Related AEs by SOC, PT, and Analysis Period

5.6.2.3 Deaths

The number and percentage of subjects who died due to treatment-emergent adverse events will be summarized by preferred term and relationship to study treatment. All deaths will be presented in a separate listing along with primary cause.

All deaths and primary cause of death as reported on the eCRF death form will be summarized. In addition, deaths occurring within/after 60 days of last study treatment dose or within 60 days of first study treatment dose and primary cause of death will be summarized.

A listing of all deaths will be provided.

5.6.2.4 AEs of Special Interest and Other AEs of Clinical Interest

AESIs and other AEs of clinical interest, including the identified and potential risks of epcoritamab, and the criteria for identifying these events are presented in Table 9.

Table 9 AESIs and Other AEs of Clinical Interest with Search Criteria

Safety Topic of Interest	MedDRA Query	Broad or Narrow Search	Code / Search Criteria

Safety Topic of Interest	MedDRA Query	Broad or Narrow Search	Code / Search Criteria
CRS (AESI)*	PT	N/A	10052015 Cytokine release syndrome 10050685 Cytokine storm
ICANS (AESI)*	PT	N/A	10083347 Immune effector cell-associated neurotoxicity syndrome
CTLS (AESI)	LLT	N/A	10078187 Clinical tumour lysis syndrome 10078189 Clinical tumor lysis syndrome
Neurological events (broad definition)	SOC	N/A	10029205 Nervous system disorders 10037175 Psychiatric disorders
Neurological events (Topp definition)	HLGT	N/A	10011305 Cranial nerve disorders (excl neoplasms) 10012221 Deliria (incl confusion) 10013511 Disturbances in thinking and perception 10014623 Encephalopathies 10057167 Mental impairment disorders 10028037 Movement disorders (incl parkinsonism) 10029305 Neurological disorders NEC 10029317 Neuromuscular disorders 10034726 Personality disorders and disturbances in behaviour 10037176 Psychiatric disorders NEC 10039911 Seizures (incl subtypes)
Infections	SOC	N/A	SOC 10021881 Infections and Infestations
Serious infections*	SOC	N/A	Serious Events in SOC 10021881 Infections and Infestations
COVID-19	SMQ	Narrow	20000237 COVID-19
Cardiac disorders	SOC	N/A	SOC Cardiac disorders
Gastrointestinal disorders	SOC	N/A	SOC Gastrointestinal disorders
Leukopenia (broad)	SMQ	Broad	20000030 Haematopoietic leukopenia
Leukopenia (grouped)	PT	N/A	10024384 Leukopenia 10047942 White blood cell count decreased
Neutropenia (grouped)	PT	N/A	10029354 Neutropenia 10029366 Neutrophil count decreased
Febrile neutropenia	PT	N/A	10016288 Febrile neutropenia
Lymphopenia (grouped)	PT	N/A	10025256 Lymphocyte count decreased 10025327 Lymphopenia
Thrombocytopenia (broad)	SMQ	Broad	20000031 Haematopoietic thrombocytopenia
Thrombocytopenia (grouped)	PT	N/A	10035528 Platelet count decreased 10043554 Thrombocytopenia
Anemia (broad)	SMQ	Broad	20000029 Haematopoietic erythropenia

Safety Topic of Interest	MedDRA Query	Broad or Narrow Search	Code / Search Criteria
Anemia (grouped)	PT	N/A	10002034 Anaemia 10018838 Haematocrit decreased 10018884 Haemoglobin decreased 10038153 Red blood cell count decreased 10040249 Serum ferritin decreased
Injection site reactions	HLT	N/A	10022097 Injection site reactions
Pyrexia	PT	N/A	10005911 Body temperature increased 10037660 Pyrexia
Tumour flare	PT	N/A	10045169 Tumour flare
Haemophagocytic lymphohistiocytosis	PT	N/A	10071583 Haemophagocytic lymphohistiocytosis (includes LLT Macrophage activation syndrome) 10090214 Immune effector cell-associated haematotoxicity 10089622 Immune effector cell-associated HLH-like syndrome 10040247 Serum ferritin abnormal 10040250 Serum ferritin increased 10075046 Hyperferritinaemia
Progressive multifocal leukoencephalopathy	PT	N/A	10078957 JC virus CSF test positive 10074361 JC virus granule cell neuronopathy 10023163 JC virus infection 10036807 Progressive multifocal leukoencephalopathy 10057366 Human polyomavirus infection 10070356 JC polyomavirus test positive 10024382 Leukoencephalopathy 10048999 Leukoencephalomyelitis 10070342 Polyomavirus test positive
Second Primary Malignancy	SMQ PT	Narrow N/A	20000091 Malignant or unspecified tumours 10028537 Myelofibrosis 10028561 Myeloid metaplasia 10028533 Myelodysplastic syndrome 10067387 Myelodysplastic syndrome transformation 10028535 Myelodysplastic syndrome unclassifiable 10088023 Myelodysplastic syndrome with excess blasts 10088022 Myelodysplastic syndrome with multilineage dysplasia 10088024 Myelodysplastic syndrome with ringed sideroblasts 10088025 Myelodysplastic syndrome with single lineage dysplasia 10090858 Myelodysplastic syndrome /myeloproliferative neoplasm overlap syndrome
Medication error	SMQ	Broad	20000224 Medication error

Safety Topic of Interest	MedDRA Query	Broad or Narrow Search	Code / Search Criteria
Severe cutaneous adverse reactions	SMQ	Broad	20000020 Severe cutaneous adverse reactions

*Important identified risk.

5.6.2.4.1 CRS

Both subject-level and event-level summaries will be provided for CRS. The following subject-level summaries will be provided:

- CRS maximum grade (1 to 5)
- Occurrence of any CRS signs and symptoms (fever, hypotension, hypoxia, and other)
- Treatment with oxygen, vasopressor, anti-cytokine therapy, and corticosteroids for CRS
- CRS leading to dose modifications
- CRS leading to drug discontinuation
- Time to CRS event onset from the most recent dosing (days)
- Time to CRS resolution (days) for subjects with resolved events

The percentages for CRS maximum grade will be relative to the number of subjects in the analysis set, while the percentages for occurrence of any CRS signs and symptoms and treatment with anti-cytokine therapy or corticosteroids will be relative to the number of subjects with at least 1 CRS event.

The following event-level summaries will be provided:

- Number of episodes per subject (1, 2, 3, etc.)
- CRS maximum grade (1 to 5)
- Occurrence of any CRS signs and symptoms (fever, hypotension, hypoxia, and other)
- Treatment with anti-cytokine therapy or corticosteroids for CRS
- CRS leading to dose modifications
- CRS leading to drug discontinuation
- Time to CRS event onset from the most recent dosing (days)
- Time to CRS event resolution (days)

The percentages for number of episodes per subject will be relative to the number of subjects with at least 1 CRS event, while other percentages will be relative to the number of CRS events in the analysis set.

CRS events will also be summarized by dosing period (priming, intermediate, first full, second full, and third full and after) for the subject-level and event-level analyses.

The longest recorded duration CRS will be used for subjects with >1 CRS event.

A listing of CRS events will be provided.

5.6.2.4.2 ICANS

The following summaries will be provided for ICANS:

- ICANS maximum grade (1 to 5)
- Worst on-treatment ICE score (0-2, 3-6, 7-9, 10)
- ICANS leading to dose modification
- ICANS leading to drug discontinuation
- Time from first dose to first ICANS onset (days)
- Time from most recent dose to ICANS onset (days)
- Time to resolution (days) for subjects with resolved events

A listing of ICANS events will be provided.

5.6.2.4.3 Clinical Tumor Lysis Syndrome (CTLS)

The following summaries will be provided for CTLS events:

- CTLS maximum grade (1 to 5)
- CTLS leading to dose modification
- CTLS leading to drug discontinuation
- Time from first dose to first CTLS onset (days)
- Time from most recent dose to CTLS onset (days)
- Time to resolution (days) for subjects with resolved events

A listing of CTLS events will be provided.

5.6.2.4.4 Adverse Events of Clinical Interest

AEs of clinical interest (see Table 9) will be summarized by SOC and PT. Additionally, the following summaries will be provided for each safety topic at subject level:

- Maximum grade (1 to 5)
- Number of episodes per subject (1, 2, 3, etc.)
- Subjects with event requiring treatment
- Time from first dose to first onset (days)
- Time to resolution (days) for subjects (with all events resolved)

The percentages for number of episodes per subject will be relative to the number of subjects with at least one event, while the percentage for maximum grade will be relative to the number of subjects in the analysis set.

5.6.3 Additional Safety Assessments

5.6.3.1 Laboratory Results

The evaluation of laboratory results will focus on the following selected analytes:

- Hematology: hemoglobin, white blood cell, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), international normalized ratio, activated partial thromboplastin time, and platelets.

- Chemistry: sodium, potassium, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), LDH, total bilirubin, uric acid, phosphate, calcium, glucose, magnesium, and albumin.

Descriptive statistics will be used to summarize observed laboratory values and change from baseline in observed value over time. The treatment-emergent (worsened during treatment period) worst toxicity grade during treatment according to CTCAE version 5.0, any grade and grade 3-4, will be summarized. Shift tables from baseline to worst toxicity grade during treatment will also be provided for each laboratory analyte listed above. Line plot of median with percentiles over time for selected laboratory analyte may be produced, as applicable.

In addition, a listing of subjects with any abnormal laboratory results will be provided.

5.6.3.2 Vital Signs and Physical Examination

Vital signs results over time will be summarized descriptively. Incidence of clinically notable (refer to below definition) vital signs results will be reported. A separate table will present the number and percent of subjects meeting these criteria, overall and by visit.

Definition of clinically notable elevated vital sign values:
- Systolic blood pressure (BP): ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline
- Weight: Increase of ≥ 10% from baseline
- Heart rate: ≥ 120 bpm with an increase of ≥ 15 bpm from baseline
- Temperature: >38° C

Definition of clinically notable decreased vital sign values:
- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Weight: decrease of ≥ 10% from baseline
- Heart rate: ≤ 50 bpm and a decrease ≥ 15 bpm from baseline
- Temperature: < 35° C
- Pulse oximetry: <92% oxygen saturation

5.6.3.3 Electrocardiogram (ECG)

The number and percentage of subjects with abnormal ECG findings will be summarized.

QTcF will be categorized as defined in International Conference on Harmonization (ICH) E14: <=450 ms, >450-480 ms, >480-500 ms, and >500ms.

5.6.3.4 ECOG Performance Score

Frequencies of ECOG score will be reported over time. Shift table from baseline to worst score during the treatment will be provided.

5.7 Other Analyses

5.7.1 Pharmacokinetics (PK)

Descriptive statistics, coefficient variation and geometric mean will be provided to summarize epcoritamab PK concentrations over time. A plot of mean (±SD) epcoritamab serum concentrations over time will be provided.

5.7.2 Immunogenicity

The incidence of anti-epcoritamab antibodies (immunogenicity) will be summarized.

5.7.3 Pharmacokinetics/Pharmacodynamics

If sufficient data are available, pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of epcoritamab and efficacy endpoints. If analysis is to be performed, details and results of the analysis will be presented in a separate report.

5.7.4 Biomarkers

Descriptive summary for selected biomarker parameters over time will be tabulated, and where appropriate, plotted.

Correlation between selected biomarker expression levels at baseline or changes in biomarker expression levels from baseline and efficacy endpoints (response or time-to-event), may be performed. If sufficient data are available, the prognostic effect of achieving MRD negative status on PFS and OS will be investigated.

Results of biomarker analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

5.7.5 PRO/Health Economics

Analyses of PRO endpoints will be conducted on subjects in the PRO analysis set.

Compliance rates for completion of all questionnaires at each time point will be summarized based on number of expected and out of the number in the ITT analysis set.

5.7.5.1 FACT-Lym

The FACT-Lym (Version 4) is a 42-item questionnaire to assess the quality of life in patients with lymphoma (See Protocol). It consists of a 27-item component focused on general quality of life and a 15-item lymphoma-specific module. The FACT-Lym elicits patient responses to general quality of life and lymphoma specific statements using a 5-point rating scale (not at all, a little, somewhat, quite a bit, very much) and a 7-day recall period. The items and their corresponding responses are grouped into 5 subscales: Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB), Functional Well-Being (FWB), and Lymphoma subscale (LymS). Scores will be generated for each of the subscales. The PWB subscale (7 items) and the LymS subscale (15 items) have all items in these subscales reverse coded/scored where 4 = "not at all" to 0 = "very much". The SWB subscale (7 items) and the FWB subscale (7 items) have items scored in the form 0 = "not at all" to 4 = "very much". The EWB subscale (6 items) has one item that is reverse coded (i.e., 4 = "not at all" to 0 = "very much") and 5 items that are scored from 0 = "not at all" to 4 = "very much". Scores for each subscale will be obtained from the sum of item scores within the subscale multiplied by the number of items in the subscale and divided by the number of items answered for that given subscale. The subscale scores range from 0-28 for PWB, 0-28 for SWB, 0-24 for EWB, 0-28 for FWB, and 0-60 for LymS.

In addition, the following scores will be derived:

- The FACT-Lymphoma Trial Outcome Index (TOI) from the sum of the PWB score, the FWB score and the LymS score yielding TOI scores ranging from 0 to 116.
- The FACT-G total score from the sum of PWB score, SWB score, EWB score, and FWB score yielding FACT-G scores ranging from 0 to 108.
- The FACT-Lym total score from PWB score, SWB score, EWB score, FWB score, and LymS score yielding FACT-Lym scores ranging from 0 to 168.

Higher scores represent a better quality of life.

For each of these scores, descriptive statistics at baseline and post-baseline assessments over time will be reported by treatment group. In the event of missing item(s) in a FACT-Lym assessment, the subscale scores will be computed according to the FACT scoring and administration guidelines by multiplying the sum of the subscale by the number of items in the subscale then dividing by the number of items actually answered.

Analysis of treatment effect by week 12: To assess the treatment effect on PRO outcomes after 12 weeks, a mixed model with subject random effect will be fit using the PRO outcomes for the

subscales and total scores indicated above as the response variables. Analysis will include subjects with baseline and at least one postbaseline score and will include data up to the end of 12 weeks (i.e., Day 1 of Cycle 4 for epcoritamab and R-GemOx and Day 1 of Cycle 5 for BR). The model will include treatment, baseline score, visit, and the randomization stratification variables as covariate. A first order auto-regressive covariance matrix [AR(1)] will be tested to model the within-subject error. The model-based least squares estimate of mean change from baseline to week 12 (Lsmean) will be computed for each treatment, as well as the difference between treatments, along with the p-value and associated 95% confidence intervals. Sensitivity analyses examining the missing data assumptions may be conducted.

The minimally important difference (MID) is the smallest change in PRO scores deemed as important and will be used as within-person meaningful threshold of change. An improvement for any particular PRO outcome will be defined as an improvement in score relative to baseline that equals to or exceeds the MID thresholds defined as:

FACT-Lym Subscale Score	Range	MID published range
FACT-G total (Webster et al, 2003)	0-108	3–7
FACT-LymS (Carter et al, 2008)	0-60	2.9–5.4
FACT-Lym TOI (Carter et al, 2008)	0-116	5.5-11
FACT-Lym total (Carter et al, 2008)	0-168	6.5-11.2

A PRO responder event will be defined as a change from baseline to time point in follow-up where the improvement in the score of a given subscale is greater than the lower bound of the published MID range. Newly developed MID thresholds may be considered based on analyses of data from other Epcoritamab trials involving DLBCL subjects.

An analysis of PRO responders will be conducted by comparing the proportion of PRO responders (i.e., proportion of subjects whose change from baseline to week 12 is equal or greater than the pre-defined meaningful within-subject change values) between treatment groups by week 12. Stratified exact CMH test will be used to test the difference in proportion of responders between treatment groups. The CMH estimate of odds ratio of achieving PRO response, together with its 95% CI, and p-value for testing treatment difference will be provided. An unstratified analysis may also be conducted. In addition, time-to-improvement analysis may be performed to support the corresponding PRO responder analysis.

5.7.5.2 EQ-5D-3L

The change in EQ-5D scores will be analyzed using RMMM with subject random effect using the EQ-5D utility scores and the visual analogue scale (VAS) indicated above as the response

variables. Each model will include subjects with baseline and at least one postbaseline score and will include data up to the end of 12 weeks (i.e., Day 1 of Cycle 4 for epcoritamab and R-GemOx and Day 1 of Cycle 5 for BR), similar to the approach in Section 5.7.5.1. Models will include treatment, visit, and the randomization stratification variables. The least squares (LS) mean change from baseline at 12 weeks and the difference between treatments will be presented along with the p-value and associated 95% confidence intervals. Sensitivity analyses examining the missing data assumptions may be conducted.

5.7.5.3 TASQ

Analyses for TASQ questionnaire will be specified in a supplementary SAP and may be reported separately.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1: Changes to Protocol-planned Analyses

Time to complete response (TTCR) and duration of complete response (DOCR) will be analyzed as supportive secondary endpoints.

6.2 Appendix 2: Definition of Baseline

Baseline value is defined as the last observation on or prior to the first dosing or last observation prior to randomization date (for non-treated subjects).

For analysis purpose, baseline period will include the following evaluations or events:

- Evaluations or events occur before the date and time of the first dose of trial treatment
- Evaluations on the same date of the first dose of trial treatment but the time component (onset time of event or evaluation time and dosing time) is missing or not collected, then the following definitions will apply.
    - Laboratory tests, vital signs (including weight and height), ECOG performance status, and constitutional symptoms on the same date of the first dose of trial treatment will be considered as baseline evaluations.
    - Adverse events onset on the same date of the first dose of trial treatment will not be considered as pre-treatment events.

If there are multiple valid assessments, the assessment that is closest to the day (and time if collected) of the first dose of trial treatment will be used as the baseline in the analyses. If multiple assessments are collected on the same date (and time if collected), the assessment with the latest visit will be considered as baseline, unless stated otherwise.

Similarly, for analysis purpose, on-treatment period will include:

- On-treatment AEs as defined for those AEs onset during on-treatment period (onset date and time on or after the date and time of first dose of trial treatment or with an onset date on and after the day of first dose of trial treatment if time is not collected or is missing), and AEs with onset date and time prior to the first dose of trial treatment and worsening during on-treatment period.
- On-treatment evaluations (laboratory tests, vital signs, ECOG performance status, constitutional symptoms, etc.) will be defined as evaluations taken during on-treatment period (after the day [and time if collected and not missing] of first dose of trial treatment).

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

6.3 Appendix 3: Data Monitoring Committee

This trial will institute an IDMC, consisting of clinicians and at least 1 statistician, which will function independently of all other individuals associated with the conduct of this clinical trial, including the investigators participating in the trial. The functions and responsibilities of the IDMC are described in the IDMC Charter, which will be approved by the IDMC.

The IDMC will review cumulative safety data after 40 subjects (approximately 20 in the epcoritamab arm) have been treated for at least 1 cycle, and approximately every 4 months thereafter during the trial. The IDMC will also be available on an ad hoc basis, i.e., to advise and recommend actions in relation to urgent safety signals, mitigation plans, etc. or if requested by the Sponsor Safety Committee (SSC) (refer to IDMC Charter).

7 REFERENCES

Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41:582-92