Protocol Number: ADCT-402-103

Official Title: A Phase 1/2 Open-Label Study to Evaluate the Safety and Efficacy of Loncastuximab Tesirine and Ibrutinib in Patients with Advanced Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma (LOTIS-3)

NCT Number: NCT03684694

Document Date: 28 March 2023

Statistical Analysis Plan

A Phase 1/2 Open-Label Study to Evaluate the Safety and Efficacy of Loncastuximab Tesirine and Ibrutinib in Patients with Advanced Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma (LOTIS-3)

PROTOCOL NO.: ADCT-402-103

SAP Version No./ Date: 1.0/ 28, Mar 2023

Statistician: [redacted]

Confidentiality Statement

SAP Approval – Sponsor Signatory

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SAP accepted and approved by:

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ADC Therapeutics [redacted]

Signature Date

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VP, Head of Biometrics
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Signature Date

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Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
BOR	Best overall response
C1D1	Cycle 1 Day 1
CI	Confidence interval
[redacted]	[redacted]
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DESC	Dose Escalation Steering Committee
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
EOT	End of Treatment
IP	Investigational product
IRC	Independent Review Committee
IV	Intravenous
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response

PT	Preferred term
QTc	Corrected QT interval
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
SPD	Sum of Product of the Perpendicular Diameters
std	Standard deviation
TEAE	Treatment-emergent adverse event
TANT	Tumor-associated non tumor
WHODRUG DD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under ADC Therapeutics Protocol ADCT-402-103.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the Protocol Amendment 5 dated 31 August 2021.

Since this study was early terminated due to lack of efficacy singnal. The current number of patients will be reduced in Phase 1 dose escalation , Phase 1 does expansion, and Phase 2.

2 Study Objectives

2.1 Primary Objectives

Phase 1:

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

Phase 2:

- To evaluate the efficacy of loncastuximab tesirine given at every cycle in combination with ibrutinib in patients with relapsed or refractory DLBCL

2.2 Secondary Objectives

Phase 1:

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

Phase 2:

- To further evaluate the safety and efficacy of loncastuximab tesirine in combination with ibrutinib in non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients
- To further evaluate the PK profile and immunogenicity of loncastuximab tesirine when given in combination with ibrutinib
- To evaluate the impact of the combination on patient-reported outcomes (PROs)

3 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Secondary	
Phase 1: • To evaluate the antitumor effect of the combination of loncastuximab tesirine with ibrutinib • To characterize the PK profile of loncastuximab tesirine when given in combination with ibrutinib • To evaluate the immunogenicity of loncastuximab tesirine when given in combination with ibrutinib **Phase 2:** • To further evaluate the safety and efficacy of loncastuximab tesirine in combination with ibrutinib in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients • To further evaluate the PK profile and immunogenicity of loncastuximab tesirine when given in combination with ibrutinib • To evaluate the impact of the combination on patient-reported outcomes (PROs)	**Phase 1:** Overall response rate (ORR) according to the 2014 Lugano classification as determined by Investigator. ORR defined as the proportion of patients with a BOR of CR or partial response (PR) Phase 1 and Phase 2 **Phase 1 and Phase 2:** Duration of response (DOR) defined as the time from the documentation of first tumor response to disease progression or death, in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients Relapse-free survival (RFS) defined as the time from the documentation of CR to disease progression or death in in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients Progression-free survival (PFS) defined as the time between start of treatment and the first documentation of progression, or death in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients Overall survival (OS) defined as the time between the start of treatment and death from any cause in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients Concentrations and PK parameters of loncastuximab tesirine (total antibody, pyrrolobenzodiazepine (PBD)-conjugated antibody, and unconjugated cytotoxin SG3199) in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients Anti-drug antibody (ADA) titers and, if applicable, neutralizing activity to loncastuximab tesirine in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients **Phase 2:** ORR according to the 2014 Lugano classification in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients. ORR defined as the proportion of patients with a BOR of CR or PR for all treated patients. ORR is determined by IRC and/or Investigator. CRR according to the 2014 Lugano classification(Cheson et al., 2014) as determined by IRC and/or Investigator in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients CRR according to the 2014 Lugano classification(Cheson et al., 2014) as determined by investigator in the non-GCB DLBCL patient Frequency and severity of AEs and SAEs in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients Change from baseline of safety laboratory values, vital signs, ECOG performance status, and 12-lead ECGs in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients Change from baseline in PROs as measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, LymS of FACT4-ym, and EQ-5D-5L, in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients

4 Study Design

This is a Phase 1/2 open-label single-arm combination study, with a dose escalation Phase 1 followed by Phase 2. The study will enroll approximately 136 patients.

Phase 1:

A standard 3+3 dose escalation design will be used. The DLT Period will be the first 21 days of ibrutinib treatment. The dose escalation cohort will receive loncastuximab tesirine for 2 cycles with concurrent ibrutinib (concomitant therapy) and may then continue ibrutinib therapy up to 1 year.An additional dose level of 75 μg/kg loncastuximab tesirine will be explored and evaluated during this phase of the study.

A Dose Escalation Steering Committee (DESC) composed of study investigators and ADC Therapeutics personnel will be responsible for decisions concerning dose escalation. At the discretion of the DESC, enrollment may be expanded to further evaluate safety and efficacy at any dose level that has completed the 3+3 dose escalation cohort with no more than 1 DLT in 6 patients. Additional patients may be added only if there is at least 1 patient with documented PR or CR.

No more than 10 patients in each of the 2 treatment cohorts (GCB DLBCL and MCL) can be treated at the expanded enrollment portion of Phase 1, and up to 20 patients will be treated in the non-GCB DLBCL cohort. This will allow the trial to enroll approximately 40 patients among the 3 expanded cohorts.

When the maximum tolerated dose (MTD) or Recommended Phase 2 Dose (RP2D) is defined there will be an efficacy and safety evaluation made by the Sponsor in consultation with investigators to determine benefit risk of the combination therapy.Once MTD or RP2D is determined and if there is a ≥10% improvement observed in CRR or ORR in any of the treatment cohorts in all DLBCL, non-GCB, GCB, or MCL when compared to the loncastuximab tesirine monotherapy, along with an acceptable safety profile, then Phase 2 of the study will commence.

Patients who have a response of PR or stable disease (SD) at the 14-week disease assessment may receive 2 additional doses of loncastuximab tesirine given 4 weeks apart (C5D1 and C6D1) . Ibrutinib will be administered orally at 560 mg once daily continuously during all cycles containing ibrutinib.

Phase 2:

Once the dose level of loncastuximab tesirine has been defined, the Phase 2 portion of the study will enroll in 3 separate cohorts: non-GCB DLBCL, GCB DLBCL, and MCL.

Each of the cohorts will be treated at the RP2D dose of loncastuximab tesirine determined in Phase 1 and ibrutinib. An IRC will be used in all cohorts to evaluate the response to the combination therapy.

Loncastuximab tesirine will be administered on C1D1 and C2D1. Patients who have a response of CR, PR, and SD at later disease assessments (Week 14 and Week 30) will receive additional doses of loncastuximab tesirine on C5D1, C6D1, C9D1, and C10D1. Ibrutinib will be administrated orally at 560 mg once daily continuously during all cycles.In the non-GCB DLBCL cohort, a Simon's 2-stage design will be used with an interim analysis for futility on the first 22 patients. If ≥6 patients achieve CR, this cohort will proceed to complete full enrollment. Enrollment will continue during the interim analysis; however, further enrollment in this cohort will be halted if futility is confirmed.

As of the data cutoff April 21, 2021, the interim analysis for non-GCB and GCB DLBCL cohorts was performed and the futility on non-GCB DLBCL was not met.

Subsequent to the interim analysis showing the potential of every cycle dosing of loncastuximab tesirine (see Protocol Section 2.2), the following will be performed:

- RP2D will be re-determined by DESC.

- Enrollment of the non-GCB DLBCL cohort treated with the combination of loncastuximab tesirine administered at an intermittent dose schedule and daily ibrutinib will be closed. GCB and MCL will complete the enrollment target set forth in the initial phase 2 design and remain under the initial treatment schedule.

- A new Phase 2 cohort of approximately 100 R/R DLBCL patients (with at least 40 patients each of GCB and non-GCB) will be introduced at the re-determined RP2D of loncastuximab tesirine administered in every cycle in combination with ibrutinib po daily given.

Patients will receive loncastuximab tesirine Q3W on Day 1 of first 2 cycles, followed by Q4W on Day 1 of every subsequent cycles. Ibrutinib will be administered at 560 mg po daily for first two cycles, then a dose reduction to 420 mg po daily for subsequent cycles.

A two-stage design with futility monitoring will be used for this new Phase 2 cohort. In the first stage, 60 patients will be accrued. If there are 20 or fewer CRs in these 60 patients, this cohort will be stopped. Otherwise, 40 additional patients will be accrued for a total of 100.

The study will include a Screening Period (of up to 28 days), a Treatment Period (cycles of 3 to 4 weeks), and a Follow-up Period (approximately every 12-week visits for up to 2 years after treatment discontinuation). On March 3, 2022, ADC Therapeutics announced to discontinue the study. The new Phase 2 cohort will be not enrolled.

4.1 Sample Size Consideration

There will be 136 patients for the entire study.

Phase 1:

47 patients will be treated with the combination of loncastuximab tesirine and ibrutinib.

Phase 2:

89 patients will be treated during Phase 2 study.

The 89 patients will be treated with the combination of loncastuximab tesirine and ibrutinib in three different cohorts:

- 49 Non-GCB DLBCL was to enroll and treated interim data analysis for futility. The study will close with approximately 48 patients.
- GCB DLBCL cohort will enroll approximately 30 patients, and
- MCL cohort will enroll approximately 10 patients

Approximately 100 R/R DLBCL patients with at least 40 patients each for GCB and non-GCB will be accrued to the new treatment cohort where loncastuximab tesirine is given at every cycle with ibrutinib po daily.

Phase 2 Sample Size Justification for the non-GCB DLBCL Cohort Where Loncastuximab Tesirine is Given Intermittently in Combination with Ibrutinib

The primary hypothesis is that the CRR based on central review for patients treated with loncastuximab tesirine and ibrutinib is significantly greater than 20% (i.e., H_0: $p \leq 0.2$ vs. H_a: $p > 0.2$). This hypothesis will be tested at type I error of 0.05 (two sided).

Simon's 2-stage design (Simon, 1989) will be used for Phase 2 non-GCB DLBCL cohort. The null hypothesis that the true CRR is 0.2 will be tested against a one-sided alternative. In the first stage, 22 patients will be accrued. If there are 5 or fewer CRs in these 22 patients, this cohort will be stopped. Otherwise, 44 additional patients will be accrued for a total of 66. The null hypothesis will be rejected if 20 or more CRs are observed in 66 patients. This design yields a type I error rate of 0.05 and power of 90% when the true CRR is 0.4.

Phase 2 Sample Size Calculation for the Cohort Where Loncastuximab Tesirine is Given at Every Cycle in Combination with Ibrutinib

The primary hypothesis is that the CRR is based on central review for patients treated with the re-determined RP2D of loncastuximab tesirine and ibrutinib combination is significantly greater than 30% (i.e., H_0: $p \leq 0.3$ vs. H_a: $p > 0.3$). This hypothesis will be tested at type I error of 0.05 (two sided).

A two-stage design with futility monitoring (Zeng et al., 2015) will be used. The null hypothesis that the true CRR is 0.3 will be tested against a one-sided alternative. In the first stage, 60 patients will be accrued. If there are 20 or fewer CRs in these 60 patients, this cohort will be stopped. Otherwise, 40 additional patients will be accrued for a total of 100. The null hypothesis will be rejected if 40 or more CRs are observed in 100 patients. This design yields a type I error rate of 0.05 and power of 85% when the true CRR is 0.45. Enrollment will continue during the interim analysis.

4.2 Randomization

Not applicable.

4.3 Modifications to the statistical section of the protocol

Not applicable.

5 Statistical methods

All analyses will use SAS® version 9.4 or higher.

Unless otherwise stated, tables, listings, and figures will be broken down by cohort (non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL). Additional tables include Phase 1 tables by dose level for safety, demographic and dosing, Phase 1 tables by does level for dose escalation patients only, and tables of 60 μg/kg and 75 μg/kg loncastuximab tesirine in both Phase 1 and 2 by cohort. Tables and figures are based on the defined analysis population.

Categorical data will be presented using counts and percentages, with the number of patients in the analysis population as the denominator for percentages. Percentages will be rounded to 1 decimal place and not be displayed for zero counts.

Continuous data will be summarized using the number of observations (n), mean, standard deviation (std), median, minimum, and maximum. Minima and maxima will be rounded to the precision of the original value, and means, medians, and 95% confidence intervals (CIs) if presented will be rounded to 1 decimal place greater than the precision of the original value. The std will be rounded to 2 decimal places greater than the precision of the original value, up to a maximum of 3 decimal places.

CI will be two-sided and use α=0.05 (i.e., 95% CIs), unless otherwise specified. For exact estimates, the CI will be calculated using the Clopper-Pearson exact method. For Kaplan-Meier estimates, the CI will be calculated using the Greenwood's formula with (complementary) log-log transformation.

Kaplan-Meier plots will be provided along with Kaplan-Meier estimates.

The Baseline value is defined as the last non-missing value or measurement taken prior to the first dose of study drug.

5.1 Analysis Populations

5.1.1 Safety Analysis Set

All patients who receive study drugs.

5.1.2 DLT-evaluable Analysis Set

All patients in Phase 1 dose escalation, who receive study drugs, excluding patients who discontinue from the study during the dose limiting toxicity (DLT) period without experiencing a DLT.

5.1.3 Efficacy Analysis Set

All patients who receive at least 1 dose of study drugs, have valid baseline disease assessment(s), and have at least one valid post-baseline disease assessment. Patients who do

not have a post-baseline assessment due to early clinical progression or death (after receiving study drugs) will also be included.

5.1.4 Pharmacokinetics (PK) Analysis Set

All patients who receive study drugs and have at least 1 pre-(C1D1) and 1 post-dose valid PK assessment.

[redacted]

5.1.6 Per Protocol Set

All patients in the Safety Analysis Set without major protocol deviations. More details are in Section 4.3.

5.2 Patient Disposition

Enrolled subjects include all patients who signed informed consent forms. All subjects enrolled, including screen fails, will be summarized. Subjects who discontinued treatment and discontinued from the study will be summarized, along with the primary reasons for discontinuation. The disposition summary will be based on the Safety Analysis Set.

Patient disposition data will be listed.

5.3 Protocol Deviations

All protocol deviations will be determined prior to database lock and will be agreed upon by a review of individual subject data. Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented before the database lock for the primary analysis.

The number and percentage of patients with any important clinical study report (CSR)-reportable protocol deviation will be summarized overall and by type of deviation. The pre-defined important CSR-reportable protocol deviations are listed below; in addition, any other protocol deviations deemed by ADCT medical to be important CSR-reportable deviations will be included in the summary.

1. Patient entered the study even though they did not satisfy the entry criteria
2. Patient received a prohibited concomitant treatment during the study
3. Patient who met criteria for mandatory study drug discontinuation during the study but did not have study drug withdrawn
4. Patient who received the wrong treatment or incorrect dose, including dose not specified in the protocol and actual dose of study drug was greater than 15% more or less than protocol planned dose.

Important protocol deviations will be summarized and listed.

5.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be tabulated for the Safety Analysis Set.

Demographic and baseline characteristics data will also be listed.

5.5 Cancer History and Medical History

Cancer history, prior radiotherapy, prior cancer surgery, prior system treatments will be tabulated for the Safety Analysis Set.

Cancer history, medical history, prior radiotherapy, prior cancer surgery, and prior system treatments will be listed.

5.6 Stem Cell Transplant

Stem cell transplant, including prior to study and on study, will be tabulated for the Safety Analysis Set.

Stem cell transplant will be listed.

5.7 Prior and Concomitant Medications (other than anticancer therapies)

All medications will be recorded in the CRF starting from the ICF signature date or from 14 days prior to C1D1, whichever is earlier, and continuing until 30 days after last dose of study drug.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) version 2019 March 01.

Prior and concomitant medications will be listed.

5.8 Exposure to Treatment

5.8.1 Extent of Study Drug Exposure

Study drug exposures will be based on the Safety Analysis Set.

A treatment cycle is defined as 3 weeks (i.e., 21 days) for Cycle 1 and Cycle 2, and then 4 weeks (i.e., 28 days) for subsequent cycles.

Duration of treatment (days) for loncastuximab tesirine, ibrutinib and both is calculated as date of last treatment – date of first treatment + 1.

Loncastuximab tesirine:

Loncastuximab tesirine will be administered as a 30-minute IV infusion on C1D1 and C2D1 per the dose escalation plan.

During Phase 1, patients who have a response of PR or SD at the 14-week disease assessment may receive 2 additional doses of loncastuximab tesirine given 4 weeks apart (C5D1 and C6D1).

During Phase 2 when loncastuximab testirine is given intermittently, patients who have a response of CR, PR, and SD at later disease assessments (Week 14 and Week 30) will receive additional doses of loncastuximab tesirine on C5D1, C6D1, C9D1, and C10D1.

During Phase 2 when loncastuximab testirine is given at every cycle, patients will receive loncastuximab tesirine Q4W on Day 1 of every subsequent cycles starting at C3.

Dose administered at each infusion (µg) for loncastuximab tesirine is calculated by concentrated investigational product (IP) volume (in mL)* 5 mg/mL *1000. For incomplete infusion, adjust the calculated prepared dose by multiplying a factor of (1- volume of dosing solution not administered [in mL]/ 50 mL). If volume of dosing solution not administered is missing, then adjust the calculated prepared dose by multiply the factor of (end time – start time [in minutes])/30 minutes.

[redacted]

Table 1 Target study day for loncastuximab tesirine

Study Visit	Target Study Day in Phase 1	Target Study Day when Loncastuximab Testirine is Given Intermittently in Phase 2	Target Study Day when Loncastuximab Testirine is Given at Every Cycle in Phase 2
C1D1	1	1	1
C2D1	22	22	22
C3D1	NA	NA	43
C4D1	NA	NA	71
C5D1	99	99	99
C6D1	127	127	127
C7D1	NA	NA	155
C8D1	NA	NA	183
C9D1	NA	211	211

C10D1	NA	239	239
C11D1	NA	NA	267
C12D1	NA	NA	295
C13D1	NA	NA	323
C14D1	NA	NA	351

Note: (1) If patients receive dose beyond C14, target study day at each cycle is calculated by adding 28 days from target study day in previous cycle. (2) Target study day calculation allows +/- 2 days window.

Duration of treatment, number of cycles dosed, total dose received (µg), total weight adjusted dose received (µg/kg), average dose per cycle (µg/kg), dose delay, reduction, and interruption, and relative dose intensity for loncastuximab tesirine will be summarized.

Ibrutinib:

During Phase 1 and Phase 2 when loncastuximab testirine is given intermittently, ibrutinib will be dispensed 560 mg orally once daily during all cycles. Relative dose intensity (%) for ibrutinib is calculated as 100 * [total dose received (mg) / duration of treatment (days) * 560 (mg/day)]

During Phase 2 when loncastuximab testirine is given at every cycle, ibruitinib will be dispensed 560 mg/day orally once daily beginning C1D1 for C1 and C2, then reduced to 420 mg/day orally once daily at C3D1 and for all subsequent cycles. Relative dose intensity (%) for ibrutinib is calculated as 100 * [total dose received (mg) / {duration of treatment (days) in C1 and C2 * 560 (mg/day) + duration of treatment (days) in all subsequent cycles * 420 (mg/day)}]

Duration of treatment, number of cycles dosed, total dose received (mg), average dose per cycle (mg), and relative dose intensity for ibrutinib will be summarized.

Exposure data and infusion details in both loncastuximab tesirine and ibrutinib will be listed.

5.8.2 Subsequent Anticancer Therapy or Procedure

Patients' subsequent anticancer therapies or procedures including systemic therapy, radiation, transplant, or other, along with the start date of new anticancer therapy or procedure will be listed.

5.9 Efficacy Analyses

Efficacy analyses will be based on the Efficacy Analysis Set. Primary efficacy analyses will also be based onPer Protocol Set.

Primary efficacy analyses will be based on CRR according to the 2014 Lugano classification (Cheson et al., 2014) as determined by independent review committee (IRC) in all DLBCL patients given loncastuximab tesirine at every cycle in combination with ibrutinib.

All efficacy endpoints and tumor assessment data will be listed.

5.9.1 Complete Response Rate

CRR is defined as the proportion of patients with a best overall response (BOR) of complete response (CR). CRR is according to the 2014 Lugano classification (Cheson et al., 2014) as determined by the IRC (Phase 2 only) and the investigator (both Phase 1 and Phase 2).

The CRR and its 95% two-sided exact CIs will be presented by the IRC and the investigator, respectively.

5.9.2 Overall Response Rate

Overall response rate (ORR) is defined as the proportion of patients with a BOR of CR or partial response (PR). ORR is according to the 2014 Lugano classification as determined by IRC (Phase 2 only) and the investigator (both Phase 1 and Phase 2).

For the analysis of ORR,

- The category of BOR includes complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and inevaluable (NE).
- Overall responses derived for BOR must be assessed on or before the start of subsequent anti-cancer therapy or procedure.
- A BOR of SD requires the patient on-study for a minimum of 35 days after the first dose of study drug. A patient with SD only before this time will be considered as NE.
- For patients who do not have post-baseline assessment due to early clinical progression or death (after receiving study drug), they will be categorized separately from patients with assessments.

Disease control rate (DCR) is defined as the proportion of patients with a BOR of CR, PR, or SD.

The ORR and DCR and their 95% two-sided exact CIs will be presented by the IRC and the investigator, respectively.

Percent change from baseline in the sum of product of the perpendicular diameters (SPD) for target lesions will be presented and also displayed as a waterfall plot, with vertical bars representing the sorted values of best percent reduction for each patient.

5.9.3 Duration of Response

Duration of response (DoR) is defined among patients with a BOR of CR or PR as the time from the documentation of first tumor response to either disease progression (based on

radiographic or clinical progression at end of treatment [EOT]/end of study [EOS]) or death due to any cause, whichever occurs first.

The censoring rules for DoR are as follow:

- For patients who are still alive at the time of analysis and without objective evidence of progression, patients will be censored at the last tumor assessment.
- For patients who receive subsequent anti-cancer therapy or procedure prior to disease progression or death, patients will be censored at the last tumor assessment prior to subsequent therapy or procedure.
- A sensitivity analysis might be considered: if a clinical progression or toxicity is observed without radiologic progression assessment confirmed, then the patient will be censored at the last tumor assessment.

The DoR will be estimated by Kaplan-Meier method. The median DoR and its 95% two-sided CI will be presented by the IRC and the investigator, respectively.

5.9.4 Relapse-Free Survival

Relapse-Free Survival (RFS) is defined as the time from the documentation of CR to either disease progression (based on radiographic or clinical progression at EOT/EOS) or death due to any cause, whichever occurs first.

The censoring rules for DoR apply to RFS.

The RFS will be estimated by Kaplan-Meier method. The median RFS and its 95% two-sided CI will be presented by the IRC and the investigator, respectively.

5.9.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the time from first dose of study drug until either disease progression (based on radiographic or clinical progression at EOT/EOS) or death due to any cause, whichever occurs first.

The censoring rules for PFS are as follow:

- For patients who are still alive at the time of analysis and without objective evidence of progression, patients will be censored at the last tumor assessment.
- For patients who receive subsequent anti-cancer therapy or procedure prior to disease progression or death, patients will be censored at the last tumor assessment on or prior to subsequent therapy or procedure.
- For patients have no post baseline tumor assessment, and have no disease progression or death, or receive subsequent anti-cancer therapy or procedure, patients will be censored at the first dose date of study drug.

- A sensitivity analysis might be considered: if a clinical progression or toxicity is observed without radiologic progression assessment confirmed, then the patient will be censored at the last tumor assessment.

The PFS will be estimated by Kaplan-Meier method. The median PFS and its 95% two-sided CI will be presented by the IRC and the investigator, respectively.

A swimmer plot will be displayed, including the points at which the criteria for response and progression by a specicific manifiestation were met (such as CR, PR, SD, PD, death, and stem cell transplant etc.).

5.9.6 Overall Survival

Overall survival (OS) is defined as the time from first dose of study drug to the date of death from any cause.

For patients who are still alive or unknown at the time of analysis, patients will be censored at the date the patient was known to be alive.

The OS will be estimated by Kaplan-Meier method. The median OS and its 95% two-sided CI will be presented.

5.9.7 Subgroup Analyses

Subgroup analyses may be performed for CRR, ORR, DoR, RFS, PFS, and OS using the following variables if appropriate:

- Demographic variables: age group, gender, race, and country
- Baseline disease characteristics: tumor staging and subtype
- Number of prior systemic therapies and response to prior systemic therapies

Other subgroup analysis factors may be evaluated as appropriate.

5.10 Safety Analyses

All safety analyses will be based on the Safety Analysis Set.

5.10.1 Adverse Events

5.10.1.1 Analyses of Adverse Events

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

The definition of SAEs is referred to the Protocol section 8.2.1.

A treatment-emergent AE (TEAE) is defined as an AE that occurs or worsens in the period extending from the first dose of study drug to 30 days after the last dose of study drug in this study or start of a new anticancer therapy, whichever is earlier.

AEs will be coded according to MedDRA Version 22.0, and the severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, where applicable.

The summary of overall TEAEs includes:

- TEAEs
- Drug-related TEAEs (loncastuximab tesirine or ibrutinib)
- Grade ≥3 TEAEs
- Drug-related Grade ≥3 TEAEs (loncastuximab tesirine or ibrutinib)
- Serious Adverse Events (SAEs)
- Drug-related SAEs (loncastuximab tesirine or ibrutinib)
- TEAEs leading to dose delayed, reduced or interrupted (loncastuximab tesirine or ibrutinib)
- TEAEs leading to discontinuation of loncastuximab tesirine or ibrutinib
- TEAEs leading to death
- Infusion related reactions

The incidence of TEAEs will be summarized by system organ class (SOC) and preferred term (PT). A patient will be counted only once within a SOC and PT, even if the patient experienced more than one AE within a specific SOC and PT. Below TEAEs will be summarized in the same fashion:

- Drug-related TEAEs by SOC and PT
- Grade ≥3 TEAEs by SOC and PT
- Drug-related Grade ≥3 TEAEs by SOC and PT
- The most common TEAEs (≥ 10% incidence) by PT
- TEAEs by SOC, PT and maximum CTCAE grade
- TEAEs by relationship to loncastuximab tesirine or ibrutinib, maximum CTCAE grade, SOC and PT

Listings of all AEs, including non-TEAEs, will be provided. Besides, TEAEs leading to dose reduced, delayed or interrupted (loncastuximab tesirine or ibrutinib), TEAEs leading to discontinuation of loncastuximab tesirine or ibrutinib, and TEAEs leading to death will also be provided.

Details on classification of AEs with missing or partial onset dates are provided in Section 6.

5.10.1.2 Dose-Limiting Toxities

Definition of DLT is referred to the Protocol section 6.4.3.

DLTs will be summarized in each dose level in the dose-escalation part for the DLT-evaluable Analysis Set.

Listings of DLTs will be provided.

5.10.1.3 Serious Adverse Events

A post-dose AE is defined as an AE during treatment that occurs or worsens from the first dose of study drug.

Below SAEs will be summarized in both TEAE and post-dose AE, respectively:

- SAEs by PT
- SAEs by SOC and PT
- SAEs by SOC, PT and maximum CTCAE grade

Listings of SAEs will be provided.

5.10.1.4 Deaths

Listings of deaths will be provided.

5.10.1.5 Adverse Events of Special Interest

Definition of adverse event of special interest (AESI) is referred to the Protocol section 8.2.2.1.

Below AESIs will be summarized in both TEAE and post-dose AE, respectively:

- AESIs by PT
- AESIs by SOC and PT
- AESIs by SOC, PT and maximum CTCAE grade

Listings of AESIs will be provided.

5.10.2 Laboratory Data

Laboratory data of hematology, chemistry, and coagulation will be summarized for the actual value and the change from baseline value at each scheduled assessment. Besides, all data will be graded according to the NCI CTCAE Version 4.0, and summarized by baseline and maximum post-baseline CTCAE grade, including unscheduled visits. Shift tables will summarize the shift from baseline grade to maximum post-baseline CTCAE grade.

Listings of laboratory data of hematology, chemistry, and coagulation will be provided. In addition, listings of urinalysis and other test, if applicable, will also be provided.

5.10.3 Electrocardiogram

Electrocardiogram (ECG) data will be summarized for the actual value and the change from baseline value at each scheduled assessment. Shift tables will summarize the shift from baseline to EOT and worst post baseline visit in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant).

Corrected QT interval by Fredericia (QTcF) will be summarized by categories as follows:

- QTcF interval > 450 ms
- QTcF interval > 480 ms
- QTcF interval > 500 ms
- QTcF interval increases from baseline > 30 ms
- QTcF interval increases from baseline > 60 ms

Listings of ECG data will be provided.

5.10.4 Vital Signs

Vital sign data, including height and weight, will be summarized for the actual value and the change from baseline value at each scheduled assessment.

Listings of vital sign data, including height and weight, will be provided.

5.10.5 ECOG Performance Status

ECOG performance status will be summarized at each scheduled assessment. Shift tables will summarize the shift from baseline to EOT and worst post baseline visit in ECOG performance status.

Listing of ECOG performance status will be provided.

5.10.6 Physical Examinations

Listings of physical examinations will be provided.

5.10.7 Pregnancy Test

Listings of pregnancy test, if applicalble, will be provided.

5.11 Patient-Reported Outcomes

Three PRO questionnaires will be assessed in Phase 2:

- European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-Core 30 (C30),
- Lymphoma subscale (LymS) of Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym),
- EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L).

Details are referred to the Protocol section 8.5.

Completion rate of each PRO questionnaire (completed questionnaires as a proportion of the expected) will be calculated. Item level missing values will be imputed as per recommendation by the instrument developers.

PRO scores for the five functional domains, eight symptoms, and global health/quality-of-life of EORTC QLQ-C30, LymS summary score of FACT-Lym, and EQ-5D-5L VAS will be summarized for the actual value and the change from baseline value at each scheduled assessment. For LymS summary score of FACT-Lym and EQ-5D-5L VAS, patients will be classified as improved/deteriorated based on the established clinically important differences for each measure. The proportion of patients with improvement/deterioration will be summarized.

Summary analyses will include data up to the start of subsequent anticancer therapy/procedure.

Data listing for each PRO questionnaire, including individual items and subscale items (if applicable), will be provided.

5.11.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a cancer health-related quality-of-life questionnaire (HRQoL) that has been widely used in clinical trials and investigations using PROs for individual patient management. It includes five functional domains (physical, emotional, social, role, and cognitive), eight symptoms (fatigue, pain, nausea/vomiting, constipation, diarrhea, insomnia, dyspnea, and appetite loss), as well as global health/quality-of-life and financial impact. Patients respond on a four-point scale from “not at all” to “very much” for most items. Most items use a “past week” recall period. Raw scores are linearly converted to a 0–100 scale with higher scores in functional and global health/quality-of-life scales reflecting better HRQoL and higher scores in symptom scales reflecting greater symptom burden. (Snyder et al, 2013, and EORTC QLQ-C30 Scoring Manual).

Based on EORTC QLQ-C30 Scoring Manual (version 3.0), the subscale scores and the algorithm to linearly converted raw scores to a 0–100 scale are detailed below.

The rule to deal with missing items is summarized as below.

- Have at least half of the items from the scale been answered?
- If Yes, use all the items that were completed, and apply the standard equations given on the previous pages for calculating the scale scores; ignore any items with missing values when making the calculations.

- If No, set scale score to missing.
- For single-item measures, set score to missing.

The SAS program for scoring the QLQ-C30 and Modules is also in the manual.

Descriptive statistics (mean, standard deviation, median, and range) of the actual values of subscale scores and changes from baseline will be presented at each scheduled assessment.

5.11.2 EQ-5D-5L

A change of 7 points in VAS from the baseline is considered the minimally important difference (MID) (Pickard et al., 2007). Patients will be classified as improved/deteriorated based on the established MID, i.e., if at least one of the post-baseline scores improves/deteriorates by the magnitude of the MID compared to baseline score. Proportion of patients with improvement/deterioration will be summarized.

Completion rate of the EQ-5D-5L will be calculated as the number of patients who complete at least one question of the EQ-5D-5L (e.g., either in descriptive system or VAS) divided by the number of patients treated at a visit. Summary of completion rate at each visit will be presented.

5.11.3 LymS of FACT-Lym

Consisting of 15 items, LymS is a subscale of FACT-Lym questionnaire that addresses symptoms and functional limitations that are important to patients with non-Hodgkin lymphoma. The patient is asked to respond to each item with a score of 0–4, where 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much.

The FACT-Lym scoring guide identifies those negatively stated items that must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from "4". After reversing proper items, all items in LymS are summed to a total. The higher score is associated with the better quality of life.

If ≤ 50% of item scores are missing, the subscale score will be calculated by multiplying the sum of the item scores by the number of items in the subscale, then divided by the number of non-missing item scores. This imputes the missing scores by the mean of the non-missing scores within a subscale.

LymS summary score = [sum of item scores] x 15/ [N of items answered]

The best change from baseline during the study, defined as the highest positive value among all post-baseline visits minus the baseline value, will also be summarized.

Based on anchor-methods, the thresholds of 4-point improvement and 5-point worsening will be considered as meaningful changes (Hlubocky et al., 2013). Patients will be classified as improved/deteriorated accordingly. Proportion of patients with improvement/deterioration will be summaried.

Completion rate of LymS will be calculated as the number of patients with sufficient number of items to calculate LymS summary score divided by the number of patients treated at a visit. Summary of completion rate at each visit will be presented.

6 Interim Analysis

In the non-GCB DLBCL cohort of Phase 2 when loncastuximab testirine is given intermittently, a Simon's 2-stage design will be used with an interim analysis for futility on the first 22 patients. If ≥6 patients achieve CR, this cohort will proceed to complete full enrollment. Enrollment will continue during the interim analysis; however, further enrollment in this cohort will be halted if futility is confirmed.

Further details are described in a separate document, Details of Futility Analysis, dated on 14 May, 2021.In the DLBCL cohort of Phase 2 when loncastuximab testirine is given at every cycle, a two-stage design with futility monitoring will be used for this new Phase 2 cohort. In the first stage, 60 patients will be accrued. If there are 20 or fewer CRs in these 60 patients, this cohort will be stopped. Otherwise, 40 additional patients will be accrued for a total of 100.

Further details are described in a separate document, Details of Two-Stage Design with Futility Monitoring, dated on yyyy-mm-dd.

7 Final Analysis

For primary and key secondary endpoints analyses, a database snapshot may be taken when 66 non-GCB DLBCL patients in Phase 2 have a minimum of 6 months follow up after initial documented response. All efficacy, safety, and PK endpoints will be analyzed and reported in the clinical study report (CSR). Results of the population PK analysis may be reported separately in a PK report. [redacted]

Follow-up analyses may be performed when all the patients complete the study per protocol.

8 Data handling conventions

8.1 General conventions

8.1.1 Missing data

In general, missing data including dates will be treated as missing and no data imputation will be applied, unless otherwise specified. Data that are potentially spurious or erroneous will be queried and examined during the review of the study data.

If there are partial or missing dates for an AE, then it will be considered as a TEAE. If the assessment of the relationship of an AE to study drug is missing, then the relationship will be as possibly related.

If the severity/grade is missing for one of the treatment emergent occurrences of an AE, the maximal severity of the remaining occurrences will be considered. If the severity is missing for all the occurrences a “missing” category will be added in summary table.

8.1.2 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline and worst values and/or grades. Re-windowing for unscheduled visits will not be performed.

8.1.3 Duplicated visits

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value per visit. Unless otherwise noted throughout the rest of this document, when a single value is needed, the following rule(s) will be used:

- If more than 1 assessment occurs during the same nominal visit, select the record closest to the nominal day for that visit.
- If there are 2 assessments that are equidistant from the nominal day, the data of the assessment after the scheduled study day will be used.
- The last measurement will be used if multiple measurements are taken on the same day.

9 Reference List

Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials* 1989;10(1):1-10.

Zeng D., Gao F., Hu K., Jia C., and Ibrahim JG, Hypothesis testing for two-stage designs with over or under enrollment, Stat Med. 2015 July 20; 34(16): 2417–2426.

ADCT-402-103 Details of Futility Analysis, 14 May 2021