Protocol Number: ADCT-402-203

Official Title: A Phase 2 Open-label Study of Loncastuximab Tesirine in Combination with Rituximab (Lonca-R) in Previously Untreated Unfit/Frail Patients with Diffuse Large B-cell Lymphoma (DLBCL) (LOTIS-9)

NCT Number: NCT05144009

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CLINICAL STUDY PROTOCOL

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A Phase 2 Open-label Study of Loncastuximab Tesirine in Combination with Rituximab (Lonca-R) in Previously Untreated Unfit/Frail Patients with Diffuse Large B-cell Lymphoma (DLBCL) (LOTIS-9)

PROTOCOL ADCT-402-203
PHASE 2

ADC Therapeutics SA
Route de la Corniche, 3B
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Switzerland

Date of Protocol Amendment 3 08 August 2022

Confidentiality Statement

Protocol Approval - Sponsor Signatory

Study Title	A Phase 2 Open-label Study of Loncastuximab Tesirine in Combination with Rituximab (Lonca-R) in Previously Untreated Unfit/Frail Patients with Diffuse Large B-cell Lymphoma (DLBCL) (LOTIS-9)
Protocol Number	ADCT-402-203
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Protocol accepted and approved by:

PPD
PPD , M.D.
PPD
ADC Therapeutics America, Inc.

PPD _____ PPD _____
Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled: "**A Phase 2 Open-label Study of Loncastuximab Tesirine in Combination with Rituximab (Lonca-R) in Previously Untreated Unfit/Frail Patients with Diffuse Large B-cell Lymphoma (DLBCL) (LOTIS-9)**" and the accompanying Investigator's Brochure (IB).

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Amendment 3, 08 Aug, 2022, the current version of International Council for Harmonisation (ICH) harmonized tripartite guideline E6: Good Clinical Practice, and all applicable governmental regulations. I will not make changes to the protocol before consulting with ADC Therapeutics or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer the study drug only to patients under my personal supervision or the supervision of a sub-Investigator.

I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ADC Therapeutics SA.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	
Institution Name	

Summary of Changes

The primary reason for this protocol amendment is to provide clarification on eligibility criteria and the simplified geriatric assessment (sGA) which must be used for assessment of fitness and fraility in patients aged ≥ 80 years.

- Section 1.2.1, Figure 1 was replaced to correct the nomenclature of one chemical element (PABC) of loncastuximab tesirine.
- Section 3, Table 3 primary objectives for cohort A and B were up-dated to align with inclusion criterion # 2 (Section 5.1).
- Section 5.1, Inclusion Criterion # 9 was amended to clarify the definition of frail patients in alignment with the simplified geriatric assessment (sGA) used in Merli, 2021, as confirmed by the main author of that publication. Accordingly, a description of sGA has been included in Section 7.2 and changes were made to the following appendices to reflect the surveys used by Merli, 2021 to perform the sGA:
  - Appendix 12.4, Katz Activities of Daily Living (ADL), the correct evaluation form as per the original publication (Katz, 1963) is now provided.
  - Appendix 12.5, Lawton-Broddy Instrumental Activities of Daily living (IADL) was replaced by a modified IADL which is based on the original publication (Lawton, 1969), but circumvents the gender bias.
  - Appendix 12.6, Cumulative Illness Rating Scale – Geriatric (CIRS-G) was replaced by a modified CIRS-G used by Parmelee, 1995.
- CCI [redacted]
- Section 5.1, Inclusion criterion # 10 was amended to clarify that this criterion is applicable for patients from ≥ 65 - < 80 years of age with cardiac comorbidities.
- Section 5.2, Exclusion criterion # 4 was removed as this aspect is covered by the inclusion criterion # 8 and # 9 (Section 5.1). This change is made to provide more clarity on eligibility.
- Schedule of Events (SoE) (Table 2), the period of reporting AEs/SAEs has been aligned with the definition in Section 8.2.
- Section 4.3, Steering Committee (SC) was added to clarify that it is in place for the study.

In addition, non-substantial clarifications/correction for inconsistencies, as well as administrative and editorial changes were included; revisions to the protocol text have also been applied to the synopsis section.

List of Prior Protocol Versions

Document	Version Date	Rationale for Changes
Protocol Amendment 2	07 March 2022	The primary reason for this protocol amendment was to provide a clarification for the exclusion criterion about prior exposure to the combination of loncastuximab tesirine and rituximab
Protocol Amendment 1	19 January 2022	The primary reason for this protocol amendment was to align the protocol with FDA comments, in particular removal of Part 2.
Protocol Original	01 November 2021	Not applicable

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List of Abbreviations

Abbreviation	Definition
β-HCG	human chorionic gonadotropin
Ab	antibodies
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BID	twice daily
BOR	best overall response
C1D1	Cycle 1, Day 1
CD19	cluster of differentiation 19
CCI	[redacted]
CI	confidence interval
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CR	complete response
CRF	case report form
CRO	contract research organization
CRR	complete response rate
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicities
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DoR	duration of response

Abbreviation	Definition
ECG	electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EoS	end of study
EoT	end of treatment
EoT CR	end of treatment complete response
EPI	elderly prognostic index
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
CCI [redacted]	
FIL	Fondazione Italiana Linfomi
FL	follicular lymphoma
FSH	follicle stimulating hormone
GCB	germinal center B-cell
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
CCI [redacted]	
GGT	gamma glutamyl transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HGBCL	high-grade B cell lymphoma
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IADL	instrumental activities of daily living
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	independent ethics committee
IPI	International Prognostic Index
IRB	institutional review board
IV	intravenous
LAR	legally authorized representative
Lonca	loncastuximab tesirine
Lonca-R	loncastuximab tesirine and rituximab
LVEF	left ventricular ejection fraction
MCL	mantle cell lymphoma
MRI	magnetic resonance imaging
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
OS	overall survival
PBD	pyrrolobenzodiazepine
PD	progressive disease
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per os (by mouth)
PR	partial response
PRO	patient reported outcome
PS	performance status
Q3W	every 3 weeks
QT	measure between Q wave and T wave in the electrocardiogram
QTcB	Bazett correction of the QT measure
QTcF	Fridericia correction of the QT measure
R	Rituximab
RBC	red blood cell
R/R	relapsed/refractory
R-CHOP	combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SC	Steering Committee
SCP	screening cut-point
SD	stable disease
sGA	simplified geriatric assessment
SoC	standard of care
SoE	schedule of events
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USPI	United States Package Insert
WBC	white blood cell
WHO	World Health Organization

Protocol Synopsis

Protocol Number:	ADCT-402-203
Title:	A Phase 2 Open-label Study of Loncastuximab Tesirine in Combination with Rituximab (Lonca-R) in Previously Untreated Unfit/Frail Patients with Diffuse Large B-cell Lymphoma (DLBCL) (LOTIS-9)
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 2
Rationale:	Diffuse large B-cell lymphoma (DLBCL) is the most frequently diagnosed non-Hodgkin's lymphoma (NHL) with more than one-third of patients 75 years or older at diagnosis. In general, patients who are ≥75 years face unique treatment challenges and experience poor outcomes due to multiple factors, including unfavorable disease biology, comorbidities, and an inability to tolerate standard first-line therapy. Additionally, up to 25% of older adults with DLBCL do not receive any first-line therapy and this number is even higher in patients ≥ 75 years of age or in patients with poor performance status. There is also a significant heterogeneity in how older patients are evaluated for fitness and ability to tolerate therapy. American Society of Clinical Oncology (ASCO) guidelines currently recommend a comprehensive geriatric assessment for all older patients > 65 years of age, however, very few studies in patients with DLBCL required a geriatric assessment tool for inclusion or to inform treatment choice. The simplified geriatric assessment (sGA) developed by the Fondazione Italiana Linfomi (FIL) identifies three distinct categories (fit, unfit, and frail) based on age, activities of daily living (ADL), instrumental activities of daily living (IADL) and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). In all age groups, including patients ≥ 75 years who are fit, standard first-line therapy consists of immuno-chemotherapy, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Unfit patients, defined (per sGA) as ≥ 80 years of age with co-existing medical conditions are often unable to tolerate full-dose R-CHOP. The current recommendation in this patient population favors the use of R-mini-CHOP (50% of R-CHOP dose) as a compromise between efficacy and safety. In the SENIOR study, the overall response rate (ORR) was 73% and the complete response (CR) rate was 53% with a 2-year progression free survival (PFS) of 56% in patients who received R-mini-CHOP. An ORR of 61.5% and CR rate of 43.5% with single-agent mosunetuzumab, a CD20 × CD3 T-cell engaging bispecific, was reported in a similar patient population. Frail patients, defined (per sGA) as ≥ 80 years of age with more significant co-existing medical conditions are often unable to tolerate R-mini-CHOP and have no definitive standard of care (SoC). There is an additional population of patients who are > 65 years of age with cardiac comorbidities that preclude the use of an anthracycline-containing regimen and for which there is no SoC. Recent studies in patients who are unable to tolerate anthracycline-containing regimens demonstrate an ORR of approximately 61% and a CR rate of 29.5% to 53% with a 2-year PFS between 38% to 49.8% There remains an unmet need to improve outcomes

for these patients by incorporating novel agents into effective regimens with improved safety and tolerability when compared to existing SoC.

Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate (ADC) directed against human cluster of differentiation 19 (CD19) that is well tolerated and has been shown to have antitumor activity in patients with relapsed/refractory (R/R) DLBCL, with ~48% of adult patients having a response. In LOTIS-1, a Phase 1 dose finding and expansion study in R/R NHL, there were 27 patients with R/R DLBCL who were ≥ 75 years of age with an ORR of 55.6% across all dose levels. In LOTIS-2, a pivotal Phase 2 single-arm study in patients with R/R DLBCL, there were 21 patients who were ≥ 75 years of age with an ORR of 52.4% and a CR rate of 38.1%.

The combination of loncastuximab tesirine and rituximab (Lonca-R) is based on preclinical evidence that the addition of rituximab to anti-CD19 ADC therapy may result in prolonged tumor control. Other clinical studies show that the addition of rituximab to standard chemotherapy regimens (e.g., CHOP, GemOx [gemcitabine and oxaliplatin]) improves efficacy.

Lonca-R is also being explored in a Phase 3 randomized study in patients with R/R DLBCL (LOTIS-5; NCT04384484).

Objectives:

Primary Objectives

Cohort A

- To assess the efficacy of a response-adapted treatment of Lonca-R in unfit patients with previously untreated DLBCL, or HGBCL, or Grade 3b FL

Cohort B

- To assess the tolerability and efficacy of a response-adapted treatment of Lonca-R in frail patients or patients with cardiac comorbidities with previously untreated DLBCL, or HGBCL, or Grade 3b FL, who are ineligible for standard R-mini-CHOP

Secondary Objectives

Cohort A and Cohort B

- Further evaluate the efficacy of Lonca-R
- To characterize the safety profile of Lonca-R
- To characterize the PK profile of Lonca when given in combination with rituximab
- To evaluate the immunogenicity of Lonca when given in combination with rituximab
- To evaluate the impact of Lonca-R treatment on treatment-related and disease-related symptoms, patient-reported functions, and overall health status

Exploratory Objectives

CCI

Endpoints:	**(Co-)Primary Endpoints** **Cohort A** • CR rate according to the 2014 Lugano Classification criteria **Cohort B** • CR rate according to the 2014 Lugano Classification criteria • Tolerability: Percentage of patients completing a total of 4 cycles of therapy divided by the total number of patients. **Secondary Endpoints** **Cohort A and B** • ORR according to the 2014 Lugano Classification • 2-yr PFS • 3-yr overall survival (3-yr OS) • Duration of response (DoR) • Frequency and severity of adverse events (AEs) and serious adverse events (SAEs) • Changes from baseline in safety laboratory variables, vital signs, physical examinations, Eastern Cooperative Oncology Group scale of performance status (ECOG PS) • Concentrations and PK parameters of loncastuximab tesirine pyrrolobenzodiazepine (PBD)-conjugated antibody, total antibody, and SG3199 unconjugated warhead • Frequency of confirmed positive anti-drug antibody (ADA) responses, their associated titers and, if applicable, neutralizing activity to loncastuximab tesirine after treatment with loncastuximab tesirine when given in combination with rituximab • Changes in patient-reported outcomes (e.g., symptoms, functions, and overall health status) from baseline as evaluated by Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) **Exploratory Endpoints** CCI [redacted]
Study Design:	This is a Phase 2, multicenter, multi-cohort, open-label study of Lonca-R in unfit/frail patients with previously untreated DLBCL. Fitness and frailty of the patients will be assessed using the sGA tool developed by the FIL. A response-adapted approach will be used in this study. Two parallel cohorts will enroll patients; Cohort A will enroll unfit patients and Cohort B will enroll frail patients or patients with cardiac comorbidities. A treatment cycle in the study is defined as 3 weeks (i.e., 21 days). Cohort A will assess efficacy and Cohort B will assess the efficacy and tolerability of Lonca-R.

After completion of 3 cycles of Lonca-R treatment, patients who achieve CR or PR will continue to receive 1 additional cycle or 3 cycles of Lonca-R, respectively. Patients in Cohort A who do not achieve a CR or PR will discontinue study treatment. For Cohort B only, patients who achieve stable disease (SD) and derive clinical benefit per the treating physician may continue to receive additional 3 cycles of Lonca-R.

Based on the results from Cohort A and/or B, a protocol amendment will be considered to further evaluate the Lonca-R combination in these patient populations.

Patient Selection:

Inclusion Criteria:

Inclusion Criteria for both cohorts:

1. Male or female
2. Pathologic diagnosis of DLBCL, as defined by the 2016 World Health Organization (WHO) classification (including patients with DLBCL transformed from indolent lymphoma), or high-grade B cell lymphoma (HGBCL), or Grade 3b follicular lymphoma (FL).
3. Measurable disease as defined by the 2014 Lugano Classification
4. Stages I-IV
5. ECOG PS 0-2; ECOG PS 3 allowed if decline in status is deemed related to lymphoma & felt to be potentially reversible by the treating physician
6. Adequate organ function as defined by screening laboratory values within the following parameters:
    a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu L$ (off growth factors at least 72 hours)
    b. Platelet count $\geq 75 \times 10^3/\mu L$ without transfusion in the past 7 days
    c. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) $\leq 2.5 \times$ the upper limit of normal (ULN)
    d. Total bilirubin $\leq 1.5 \times$ ULN (patients with known Gilbert's syndrome may have a total bilirubin up to $\leq 3 \times$ ULN)
    e. Calculated creatinine clearance > 30 mL/min by the Cockcroft and Gault equation

Note: A laboratory assessment may be repeated a maximum of two times during the screening period to confirm eligibility.

7. Women of childbearing potential (WOCBP) must agree to use a highly effective method of contraception from the time of giving informed consent until at least 12 months after the last dose of study treatment. Men with female partners who are of childbearing potential must agree to use a condom when sexually active or practice total abstinence from the time of the first dose until at least 7 months after the patient receives her/his last dose of study treatment

Inclusion Criteria specific for Cohort A:

8. Unfit as defined by the sGA (includes all of the following):
    a. Aged ≥ 80 years
    b. ADL score of 6
    c. IADL score of 8
    d. CIRS-G: no score of 3-4 and < 5 scores of 2

Inclusion Criteria specific for Cohort B:

9. Frail as defined by the sGA:
    a. Aged ≥ 80 years
    b. ADL score of < 6 and/or
    c. IADL score of < 8 and/or
    d. CIRS-G ≥ 1 score of 3-4 and/or ≥ 5 scores of 2

    OR

10. Aged ≥ 65 - <80 with at least one of the following cardiac comorbidities that make anthracycline-containing regimens inadvisable as determined by the investigator.
    a. Left ventricular ejection fraction (LVEF) ≥ 30 to < 50%
    b. History of myocardial infarction within 6 months prior to screening
    c. Ischemic heart disease
    d. History of stroke within 12 months prior to screening

Exclusion Criteria:

1. Known history of hypersensitivity to or positive serum human anti-drug antibody to a CD19 antibody
2. Previous therapy for DLBCL, HGBCL, Grade 3b FL (with exception of corticosteroid course for symptom management of less than 14 days)
3. Previous therapy with loncastuximab tesirine and rituximab for any indication
4. Known history of hypersensitivity to any component of study treatment (loncastuximab tesirine and rituximab)
5. Human immunodeficiency virus (HIV) seropositive with any of the following:
    a. CD4+ T-cell (CD4+) counts < 350 cells/µL
    b. Acquired immunodeficiency syndrome (AIDS) - defining opportunistic infection within 12 months prior to screening
    c. Not on anti-retroviral therapy, or on anti-retroviral therapy for < 4 weeks at the time of screening
    d. HIV viral load ≥ 400 copies/mL
6. Serologic evidence of chronic hepatitis B virus (HBV) infection and unable or unwilling to receive standard prophylactic antiviral therapy or with detectable HBV viral load

7. Serologic evidence of hepatitis C virus (HCV) infection without completion of curative treatment or with detectable HCV viral load
8. History of Stevens-Johnson syndrome or toxic epidermal necrolysis
9. Lymphoma with active central nervous system involvement at the time of screening, including leptomeningeal disease
10. Clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath)
11. Major surgery, radiotherapy, chemotherapy, or other anti-neoplastic therapy within 14 days prior to start of study drug (Cycle 1 Day 1 [C1D1]), except shorter if approved by the Sponsor
12. Use of any other experimental medication within 14 days prior to start of study drug (C1D1)
13. Received live vaccine within 4 weeks of C1D1
14. Congenital long QT syndrome or a corrected QTcF interval of > 480 ms at screening (unless secondary to pacemaker or bundle branch block)
15. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that the Sponsor's Medical monitor and Investigator agree, and document should not be exclusionary
16. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk

Estimated Duration of Patient Participation and Study Duration:

The duration of the study participation for each patient is defined as the time from the date of signed written informed consent to the completion of the follow-up period, withdrawal of consent, loss to follow-up, or death, whichever occurs first.

The study will include a Screening Period (up to 28 days), a Treatment Period (4-6 cycles [each of 3 weeks]), and a Follow-up Period (up to 5 years after treatment discontinuation).

After the last dose of Lonca-R, all patients will be followed every 12 weeks for 1 year, then every 24 weeks for up to 3 years, then annually up to 5 years.

The visits will be generally completed at the clinic. However, when disease assessments are not planned for a follow-up visit, the visit can be done by phone.

Patients who have progressed will be followed for survival for up to 5 years after the last dose of study drug.

The end of study occurs at the last scheduled visit/procedure for the last patient, unless the study is terminated earlier by the Sponsor.

Efficacy Assessments:	Disease assessments: positron emission tomography-computed tomography (PET-CT) Note: If the disease is not fluorodeoxyglucose (FDG)- avid at baseline, CT or magnetic resonance imaging (MRI) may be used. The assessment method determined to identify sites of disease at baseline should be used for all subsequent assessments.
Safety Assessments:	• Physical examination • ECOG PS • Height and weight • Vital signs • Pregnancy test, if applicable • Safety laboratories (hematology, chemistry, urinalysis) • AEs/SAEs, grading per Common Terminology Criteria for Adverse Events (CTCAE), version 5.0
Other Assessments:	• Patient-reported outcomes (PROs) • Blood sampling for PK, ADA CCI [redacted] • CCI [redacted]

Study Drug, Dosage, and Mode of Administration:	A treatment cycle is defined as every 3 weeks (Q3W)
	• Lonca-R
	  ○ Loncastuximab tesirine is administered in a 30-minute intravenous (IV) infusion (see Table 1 for administration schedule)
	  ○ Rituximab is administered in an IV infusion on day 1 of each cycle. Use of the subcutaneous (s.c.) formulation (Cycle 2 and beyond) or biosimilars is allowed.
	
	During the Screening Period, patients may receive pre-phase therapy with prednisone 40 mg/m^2 for up to 14 days per the treating investigator's discretion.
	
	Details of dose and administration scheme of the study are described in Table 1.

Table 1 Treatment with Lonca-R

Cohort	Treatment Regimen (1 cycle = 3 weeks [21 days])
Cohort A and Cohort B	**Lonca-R**
	Cycle 1: Day 1: Rituximab IV 375 mg/m^2 Day 2: Loncastuximab tesirine 150 µg/kg IV **Cycle 2:** Day 1:Rituximab IV* 375 mg/m^2 and loncastuximab tesirine 150 µg/kg IV **Cycles 3-4:**† Day 1: Rituximab IV* 375 mg/m^2 and loncastuximab tesirine 75 µg/kg IV

*If subcutaneous rituximab is used, the dose is 1400 mg, flat dose
†Up to 6 total cycles of Lonca-R may be administered per protocol

Granulocyte colony-stimulating factor (G-CSF) may be administered as primary prophylaxis starting with Cycle 1 of therapy and continue through each cycle of therapy for patients per the treating investigator's discretion and institution guidelines (optional).

Cycle 2 and beyond when loncastuximab tesirine and rituximab are given concomitantly, loncastuximab tesirine will be administered prior to rituximab at a dose as specified in Table 1.

Sample Size: Approximately 40 patients in Cohort A and approximately 40 patients in Cohort B

Statistical Considerations: A sample size of 40 patients for each cohort is considered adequate to assess safety and efficacy in the corresponding study population.

The percentage of ORR and CR rate with its 95% CI will be presented descriptively.

Safety analyses will be presented descriptively.

Schedule of Events

Table 2 Schedule of Events (SoE)

	Protocol Section	Screening	Treatment Period								Follow-up Period (up to 5 years from EoT)
1 cycle = 21 days			Cycle 1			Cycle 2	Cycle 3		Cycle 4-6	EoT[2]	
		Day - 28 to Day -1	Day 1	Day 2 (+2 days)	Day 9 (±2 days)	Day 1 (±2 days)	Day 1 (±2 days)	Day 15 (±2 days)	Day 1 (±2 days)		
Informed consent	7.1	X									
Eligibility criteria	5.1, 5.2	X									
Geriatric Assessment (sGA)	5.1, 7.2	X[1]									
Demography	7.2, 9.5	X									
Medical/Cancer history[3]	5.1, 9.5	X									
Physical examination	7.4.1	X	X		X	X	X		X	X	
Vital signs[4]	7.4.4	X	X	X	X	X	X		X	X	
12-lead ECG	7.4.7	X									
Height	7.4.3	X									
Weight	7.4.3	X	X		X	X	X		X	X	
ECOG PS	7.4.2	X	X			X	X			X	
CCI											

	Protocol Section	Screening	Treatment Period								Follow-up Period (up to 5 years from EoT)
1 cycle = 21 days			Cycle 1			Cycle 2	Cycle 3		Cycle 4-6	EoT[2]	
		Day - 28 to Day -1	Day 1	Day 2 (+2 days)	Day 9 (±2 days)	Day 1 (±2 days)	Day 1 (±2 days)	Day 15 (±2 days)	Day 1 (±2 days)		
Disease assessment	7.3	X[6]						X[6]	X (end of C6 only)	X[6]	X Every 12 weeks until 1 year, then every 24 weeks for 2 years then annually
Hematology and Chemistry[7]	7.4.5	X	X	X	X	X	X		X	X	
HIV, HBV, HCV status	7.4.5	X									
Urinalysis	7.4.5	X	X							X	
Pregnancy test[8]	7.4.6	X	X				X			X	X
LVEF (Echo/MUGA)	5.1	X								X	
PK sample[9]	7.5.1			X (pre-dose, Lonca EOI)		X (pre-dose, Lonca EOI)	X (pre-dose, Lonca EOI)		X (pre-dose, Lonca EOI)	X	
ADA sample[10]	7.5.2			X (pre-dose)		X (pre-dose)			X (C4 and C6 only; pre-dose)	X	

	Protocol Section	Screening	Treatment Period								Follow-up Period (up to 5 years from EoT)
1 cycle = 21 days			Cycle 1			Cycle 2	Cycle 3		Cycle 4-6	EoT[2]	
		Day - 28 to Day -1	Day 1	Day 2 (+2 days)	Day 9 (±2 days)	Day 1 (±2 days)	Day 1 (±2 days)	Day 15 (±2 days)	Day 1 (±2 days)		
CCI											
CCI											
Patient Reported Outcomes Assessment[12]	7.6		X[12]			X[12]	X[12]		X[12]	X[12]	
Optional Pre-Phase Therapy	4.2.1	X									
Lonca-R[13]											
Premedication[14]	6.4		X			X	X[14]		X[14]		
Rituximab administration	6.3		X			X	X[13]		X[13]		
Loncastuximab tesirine administration	6.3			X		X	X[13]		X[13]		
Concomitant medications	6.9	From ICF signature date or D-14, whichever is earlier, until 30 days after last dose of study treatment and as indicated for AE/SAEs thereafter.									
AEs	8	All AE/SAEs, regardless of the relationship to study treatment, will be reported from ICF signature date until 15 weeks after last dose of study treatment or the start of new anti-cancer therapy, whichever is earlier; thereafter, only related SAEs will be reported.									
Survival information										X	X

	Protocol Section	Screening	Treatment Period									Follow-up Period (up to 5 years from EoT)
1 cycle = 21 days			Cycle 1			Cycle 2		Cycle 3		Cycle 4-6	EoT[2]	
		Day - 28 to Day -1	Day 1	Day 2 (+2 days)	Day 9 (±2 days)	Day 1 (±2 days)		Day 1 (±2 days)	Day 15 (±2 days)	Day 1 (±2 days)		
First new anticancer treatment information											X	X

Note: Same SoE will be followed for all the enrolled patients irrespective of cohort of the study.

Abbreviations: AE, adverse event; CCI [redacted]; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group scale of performance status; EoT, end of treatment; CCI [redacted] CCI [redacted] HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency syndrome; ICF, informed consent form; LVEF, left ventricular ejection fraction; MUGA, multiple-gated acquisition; PET-CT, Positron emission tomography - computed tomography; SAE, serious adverse event; sGA, simplified geriatric assessment; SoE, schedule of event.

1. sGA is based on the scores of 3 surveys: ADL (Appendix 12.4), IADL (Appendix 12.5) and CIRS-G (Appendix 12.6). sGA should be done at the end of the screening period once all other eligibility criteria have been met.
2. End of Treatment visit (EoT) should occur 28 (±7) days from the last dose of study treatment, and in any case prior to the initiation of new anticancer treatment. When EoT visit coincides with a scheduled visit, the scheduled visit will become EoT visit.
3. Cancer history to include but not limited to histologic subtype, cell of origin, international prognostic index (IPI), Ann Arbor stage, extranodal involvement, bulky disease (≥ 10 cm).
4. Vital signs should include arterial blood pressure, heart rate, respiratory rate, and body temperature.

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6. Screening imaging (PET-CT) must be performed within 4 weeks prior to C1D1 and the same assessment method must be used throughout the study. Imaging should be performed at the indicated time points even if drug dosing is delayed. Imaging prior to Cycle 4 and at end of Cycle 6 should be performed within ±1 weeks of the scheduled time point; all other imaging will be performed within ±2 weeks of the scheduled time point. If a scan was performed within 6 weeks of EoT, it does not need to be repeated at the EoT visit.
7. For assessment of intermediate or high risk tumor lysis syndrome (TLS), related laboratory tests including complete blood count with white blood cells (WBC) differential, and blood chemistry (potassium, uric acid, phosphorus, calcium, lactate dehydrogenase [LDH] and creatinine) will be checked daily during first 24-72 hours after C1D1 or according to institutional routine.
8. Pregnancy test will be limited to females of childbearing potential; a final pregnancy test should be performed ≥ 12 months after the last dose of study drug has been administered (remote testing may be performed).
9. For days of loncastuximab tesirine infusion, PK will be collected predose (preferably within 2 h prior to start of infusion), and at the end (within -5 to +10 min) of Lonca infusion.
10. ADA samples will be collected predose (preferably within 2 h prior to start of infusion) on C1D2, C2D1 and then every other cycle beginning with C4. Patients who test positive for ADAs may be requested to supply additional ADA samples.

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12. PRO instrument should be completed prior to clinical assessment.
13. Patients in both cohorts will receive 1 additional cycle of assigned therapy (Cycle 4) if in CR and 3 additional cycles if PR (Cycles 4-6) based on PET-CT after Cycle 3. Patients in cohort B who achieve stable disease and are receiving clinical benefit may receive 3 additional cycles (Cycles 4-6).
14. Premedication for the Lonca-R regimen consists of dexamethasone 4 mg PO/IV BID × 3 days beginning the day prior to loncastuximab tesirine; premedication(s) for rituximab will be given according to institution standard.

Visit Scheduling Windows:

- Treatment Period: C1D1 is the reference day, otherwise visit day ± 2 days, except of visit day 2 where the time window is +2 days.
- EoT: Patients who complete all assigned treatment cycles of treatment should have their EoT visit performed 28 (±7) days from the last dose of study treatment, and in any case prior to the initiation of new anticancer treatment.
- Follow-up Period: visit day ± 14 days.

1 Introduction and Background

1.1 Diffuse Large B-cell Lymphoma and Unfit/Frail Patients

Diffuse large B-cell lymphoma (DLBCL) is the most frequently diagnosed non-Hodgkin's lymphoma (NHL) with more than one-third of patients 75 years or older at diagnosis. In general, patients who are ≥75 years face unique treatment challenges and experience poor outcomes due to a number of factors including unfavorable disease biology, comorbidities, and an inability to tolerate standard first-line therapy. Additionally, up to 25% of older adults with DLBCL do not receive any first-line therapy and this number is even higher in patients ≥75 years of age or in patients with poor performance status (Di, 2021). There is also a significant heterogeneity in how older patients are evaluated for fitness and ability to tolerate therapy. The current American Society of Clinical Oncology (ASCO) guidelines recommend a comprehensive geriatric assessment for all older patients > 65 years of age, however, very few studies in patients with DLBCL required a geriatric assessment tool for inclusion or to inform treatment choice (Tavares & Moreira, 2021). The simplified geriatric assessment (sGA) developed by the Fondazione Italiana Linfomi (FIL) identifies three distinct categories (fit, unfit, and frail) based on age, activities of daily living (ADL), instrumental activities of daily living (IADL) and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Merli, 2021; Katz, 1963; Parmelee, 1995; Lawton, 1969)

In all age groups, including patients ≥75 years who are fit, standard first-line therapy consists of immuno-chemotherapy, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) (NCCN Guidelines, 2021). Unfit patients, defined (per sGA) as ≥80 years of age with co-existing medical conditions are often unable to tolerate full-dose R-CHOP. The current recommendation in this patient population favors the use of R-mini-CHOP (50% of R-CHOP dose) as a compromise between efficacy and safety (Peyrade, 2011). In the SENIOR study by Oberic (2021), the overall response rate (ORR) was 73% and the complete response (CR) rate was 53% with a 2-year progression-free survival (PFS) of 56% in patients who received R-mini-CHOP. Olszewski (2021) reported an ORR of 61.5% and CR rate of 43.5% with single-agent mosunetuzumab, a CD20 × CD3 T-cell engaging bispecific, was reported in a similar patient population. Frail patients, defined per sGA, who are ≥ 80 years of age with more significant co-existing medical conditions are often unable to tolerate R-mini-CHOP and have no definitive standard of care (SoC) (Morrison, 2020). There is an additional population of patients who are > 65 years of age with cardiac comorbidities that preclude the use of an anthracycline-containing regimen and for which there is no SoC (Hitz, 2016; Moccia, 2021). Recent studies in patients who are unable to tolerate anthracycline-containing regimens demonstrate an ORR of approximately 61% and a CR rate of 29.5% to 53% with a 2-year PFS between 38% to 49.8% (Fields, 2014; Storti, 2018). There remains an unmet need to improve outcomes for these patients by incorporating novel agents into effective regimens with improved safety when compared to existing SoC.

Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate (ADC) directed against human cluster of differentiation 19 (CD19) that is well tolerated and has been shown to have antitumor activity in patients with relapsed or refractory (R/R) DLBCL, with ~48% of adult patients having a response.

In LOTIS-1, a Phase 1 dose-finding and expansion study in R/R NHL, there were 27 patients with R/R DLBCL who were ≥ 75 years of age with an ORR of 55.6% across all dose levels.

In LOTIS-2, a pivotal Phase 2 single-arm study in patients with R/R DLBCL, there were 21 patients who were ≥ 75 year of age with an ORR of 52.4% and a CR of 38.1%.

The addition of rituximab is based on preclinical evidence that the addition of rituximab to anti CD19 ADC therapy may result in prolonged tumor control (Ryan, 2017) and on clinical studies showing that the addition of rituximab to standard chemotherapy regimens (e.g., CHOP, GemOx [gemcitabine and oxaliplatin]) improves efficacy (Corazzelli, 2009; Habermann, 2006). As the pyrrolobenzodiazepine (PBD) component of loncastuximab tesirine produces cell death via deoxyribonucleic acid (DNA) damage in a fashion similar to many cytotoxic chemotherapy agents, the addition of rituximab is expected to produce a similar improvement in outcome and potentially result in prolonged tumor control. Rituximab will be given at the standard dose every 3 weeks (Q3W) to coincide with the administration schedule for loncastuximab tesirine to minimize the burden of therapy. This combination is also being explored in a Phase 3 randomized study in patients with R/R DLBCL (LOTIS-5; NCT04384484).

1.2 Description of the Study Drugs

1.2.1 Loncastuximab Tesirine

Loncastuximab tesirine (ADCT-402) is an ADC, composed of a humanized monoclonal antibody (RB4v1.2) directed against human CD19 conjugated through a cathepsin-cleavable linker to SG3199, a PBD dimer cytotoxin. The toxin SG3199 attached to the linker is designated as SG3249.

Pyrrolobenzodiazepines are a class of naturally occurring antitumor antibiotics found in Streptomyces. Pyrrolobenzodiazepine monomers bind in the DNA minor groove and form a single covalent aminal linkage to the exocyclic N2-amino group of guanine within purineguanine-purine sequences. Pyrrolobenzodiazepine dimers, obtained by joining two PBD monomers together via an appropriate polymethylene tether, have the ability to produce two covalent bonds forming highly cytotoxic DNA interstrand crosslinks (Hartley, 2011).

The schematic representation of loncastuximab tesirine is presented in Figure 1.

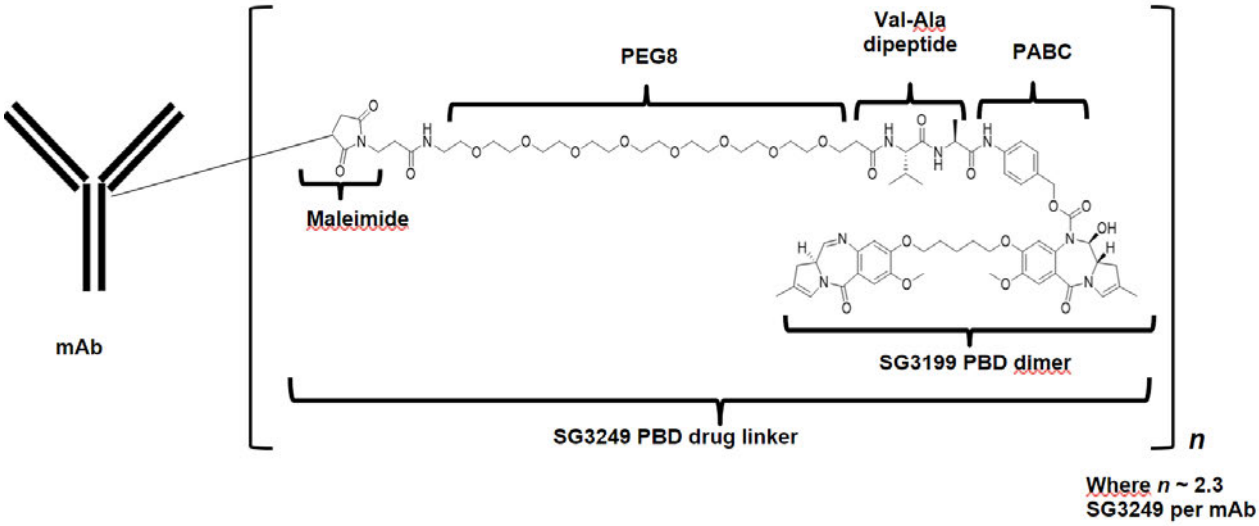

Figure 1 Schematic Representation and Chemical Structure of Loncastuximab Tesirine

Abbreviations: Ala, alanine; mAb, human monoclonal antibody being studied (RB4v1.2); PABC, para-aminobenzyl carbamate; PEG, polyethylene glycol; Val, valine.

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1.2.2 Rituximab

For rituximab or rituximab biosimilar or subcutaneous (s.c.) rituximab formulation, refer respectively to each United States Package Insert (USPI) for detailed information including safety and efficacy.

1.3 Loncastuximab Tesirine - Clinical Results

1.3.1 Phase 1 Study, ADCT-402-101

ADCT-402-101 (NCT02669017) is a first-in-human Phase 1 dose-escalation study of loncastuximab tesirine in R/R B-NHL patients, who have failed or are intolerant to established therapies, or have no other treatment options available. The study was completed with 183 patients enrolled.

Toxicity was manageable. The most common (observed in at least 5% of patients) Grade ≥ 3 treatment-emergent adverse events (TEAEs) were gamma glutamyl transferase (GGT) increased (21.3%); neutropenia (16.9%); anemia (15.3%); neutrophil count decreased (14.8%); thrombocytopenia (12.0%); platelet count decreased (10.4%). The TEAEs in 35 (19.1%) patients led to treatment discontinuation. Dose-limiting toxicities (DLT) were reported in 4 patients (3 thrombocytopenia and 1 febrile neutropenia).

Out of 180 evaluable patients with B-NHL, 48 (26.7%) achieved CR and 34 (18.9%) achieved partial response (PR), for an ORR of 82/180 (45.6%). Out of 137 evaluable patients with DLBCL, 32 (23.4%) achieved CR and 26 (19.0%) achieved PR, for an ORR of 58/137 (42.3%). Out of 14 evaluable patients with FL, 9 (64.3%) achieved CR and 2 (14.3%) achieved PR, for an ORR of 11/14 (78.6%). Out of 15 evaluable patients with mantle cell lymphoma (MCL), 5 (33.3%) achieved CR and 2 (13.3%) achieved PR, for an ORR of 7/15 (46.7%).

1.3.2 Phase 2 Study, ADCT-402-201

Study ADCT-402-201 is a Phase 2 study to evaluate the efficacy of loncastuximab tesirine used as monotherapy in patients with R/R DLBCL. The study determines the ORR according to the 2014 Lugano Classification, as well as evaluate the duration of response (DoR), CR, survival, safety, pharmacokinetics (PK), and health-related quality of life (HRQoL).

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CCI [redacted]

Additional details may be found in the current loncastuximab tesirine investigator's brochure (IB).

1.4 Benefit/Risk Assessment

Although R-mini-CHOP has anticancer activity in patients with untreated DLBCL who are unfit for full-dose R-CHOP, there is a need for regimens with an improved safety profile and better CR and PFS. In addition, there is no current SoC for patients who are frail and/or ineligible for anthracycline-based therapy. The combination of loncastuximab tesirine and rituximab is expected to provide an increased anti-tumor response however, the efficacy and safety of this combination in untreated unfit/frail patients has not been established.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of loncastuximab tesirine may be found in the current IB.

2 Study Rationale

Loncastuximab tesirine is an ADC that has been designed to target and kill CD19-expressing malignant B-cells. The Phase 1 study of loncastuximab tesirine in R/R B-cell NHL shows significant activity of loncastuximab tesirine with an acceptable safety profile in patients with R/R DLBCL, FL, and MCL (Section 1.3.1). The Phase 2 study results verified the efficacy and durability of response in heavily pretreated patients with DLBCL and was well-tolerated when administered in repeated 3-week cycles at 150 µg/kg for the first two cycles and 75 µg/kg for the subsequent cycles (Section 1.3.2). A Biologics License Application of loncastuximab tesirine for R/R DLBCL was approved by the Food and Drug Administration (FDA) on 23 April 2021.

As illustrated above, loncastuximab tesirine has single agent activity against B–NHL subtypes, including transformed lymphoma, with significant proportion of disease response in DLBCL, including complete remission. The disease course of Grade 3b FL resembles that of DLBCL and should be treated accordingly (Salaverria & Siebert, 2011). Patients with Grade 3b FL with a significant diffuse component have inferior survival outcomes similar to that of DLBCL (Hans, 2003). These patients are often excluded from clinical trials and most treatment recommendations are based on retrospective data and small case studies; the curative potential of combination chemoimmunotherapy in Grade 3b FL remains unclear (Barraclough, 2021). Including this subset of patients is consistent with current international clinical practice guidelines that identify Grade 3b FL as an aggressive lymphoma and recommend immediate treatment similar to that of DLBCL (Barraclough, 2021; Dreyling, 2020; NCCN Guidelines, 2021). The hypothesis is that loncastuximab tesirine in combination with rituximab may potentially have improved efficacy & safety for 1st line treatment in unfit/frail patients with DLBCL.

2.1 Rationale for Study Design

This is a Phase 2, multi-center adaptive design study with two parallel cohorts which will enroll in total approximately 80 unfit or frail patients with previously untreated DLBCL (respectively Cohort A and Cohort B, n = 40 patients each). The primary objective will be to determine the safety and efficacy of loncastuximab tesirine in combination with rituximab (Lonca-R) in this patient population.

An analysis for efficacy and safety in Cohorts A and B (n = 40 each) as assigned by sGA (Merli, 2021) will be conducted. The sGA is a validated objective tool to assess fitness status to predict overall survival in older patients with DLBCL.

A response-adapted approach for both cohorts will be utilized where patients in the unfit & frail cohorts who achieve a CR after 3 cycles of therapy will receive one additional cycle of therapy (4 cycles total). Patients in the unfit cohort (Cohort A) who achieve a PR after 3 cycles of therapy will receive 3 additional cycles of therapy (6 cycles total). Patients in the frail cohort (Cohort B) who achieve a PR/stable disease (SD) will receive 3 additional cycles of therapy (6 cycles total). In the patient population being evaluated, de-escalating therapy to a total of 4 cycles in patients who achieve a CR may minimize toxicity while preserving efficacy. End of

treatment CR was recently found to be highly predictive for PFS and OS in DLBCL after first-line immunochemotherapy (Kostakoglu, 2021).

2.2 Rationale for Dose Selection

In the pivotal monotherapy Phase 2 study for R/R DLBCL, ADCT-402-201, loncastuximab tesirine was dosed every 3 weeks, with 150 µg/kg for first two cycles and 75 µg/kg for the subsequent cycles, which resulted in a high level of efficacy and was well tolerated. In addition, PK analyses show that this dosing regimen resulted in comparable exposure between Cycle 1 and subsequent cycles and that this dosing regimen resulted in consistent drug exposure across cycles. The dosing regimen chosen for this study is based on the regimen of loncastuximab tesirine used in the Phase 2 study. This study will utilize the same dosing regimen for Lonca-R as the ongoing Phase 3 clinical trial LOTIS-5 comparing the Lonca-R regimen (after a safety run-in) to R-GemOx in 2L transplant-ineligible patients with DLBCL. Treatment-naïve patients will present with levels of lymphocytes (within normal limits) which are believed to function as an antigen sink to loncastuximab tesirine. Administration of rituximab is known to reduce lymphocytes levels within a day (Blasco, 2009). Therefore, loncastuximab administration in Cycle 1 is given 1 day (+2 days) after rituximab administration.

3 Study Objectives and Endpoints

Table 3 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Cohort A To assess the efficacy of a response-adapted treatment of Lonca-R in unfit patients with previously untreated DLBCL or HGBCL or Grade 3b FL. *Cohort B* • To assess the tolerability and efficacy of a response-adapted treatment of Lonca-R in frail patients or patients with cardiac comorbidities with previously untreated DLBCL or HGBCL or Grade 3b FL who are ineligible for standard R-mini-CHOP.	**(Co-)Primary Endpoints:** *Cohort A* CR rate, defined as proportion of patients with a BOR of CR according to the 2014 Lugano Classification criteria (Appendix 12.2). *Cohort B* • CR rate, defined as proportion of patients with a BOR of CR according to the 2014 Lugano Classification criteria. • Tolerability as defined by the percentage of patients completing a total of 4 cycles of therapy divided by the total number of patients.
Secondary	
Cohort A and Cohort B: • Further evaluate the efficacy of Lonca-R • To characterize the safety profile of Lonca-R • To characterize the PK profile of Lonca when given in combination with rituximab • To evaluate the immunogenicity of Lonca when given in combination with rituximab • To evaluate the impact of Lonca-R treatment on treatment-related and disease-related symptoms, patient-reported functions, and overall health status	Cohort A and Cohort B: • ORR according to the 2014 Lugano Classification, defined as the proportion of patients with a BOR of CR or PR. • 2-year PFS, defined as the proportion of patients that are PFS event-free at 2 years. • 3-yr OS, defined as the proportion of patients that are OS event-free at 3 years. • DoR defined as the time from the first documentation of tumor response (CR or PR) to disease progression or death • Frequency and severity of AEs and SAEs.

Objectives	Endpoints
	• Changes from baseline in safety laboratory variables, vital signs, physical examinations, ECOG PS • Concentrations and PK parameters of loncastuximab tesirine PBD-conjugated antibody, total antibody, and SG3199 unconjugated warhead • Frequency of confirmed positive ADA responses, their associated titers and, if applicable, neutralizing activity to loncastuximab tesirine after treatment with loncastuximab tesirine when given in combination with rituximab • Changes in patient-reported outcomes (e.g., symptoms, functions, and overall health status) from baseline as evaluated by FACT-Lym
Exploratory	
CCI	CCI

Abbreviations: ADA, anti-drug antibody; AE, adverse event; BOR, best overall response; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; EoT, end of treatment; ECOG PS, Eastern Cooperative Oncology Group scale of performance status; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; Lonca-R, loncastuximab tesirine and rituximab; ORR, overall response rate; OS, overall survival; PBD, pyrrolobenzodiazepine; PFS, progression free survival; PK, pharmacokinetic; PR, partial response; PS, performance status; R-CHOP, combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, SAE, serious adverse event.

4 Study Design

4.1 Overview

This is a Phase 2 open-label, study of Lonca-R in previously untreated unfit/frail patients with DLBCL. The study will include a Screening Period (up to 28 days), a Treatment Period (4-6 cycles [each of 3 weeks]), and a Follow-up Period (for up to 5 years after treatment discontinuation) (Section 4.2).

A response-adapted approach will be used in this study. Two parallel cohorts will enroll patients in the study. Cohort A will enroll unfit patients and Cohort B will enroll frail patients or patients with cardiac comorbidities. Cohort A will assess efficacy and Cohort B will assess the efficacy and tolerability of Lonca-R. Fitness and frailty of the patients will be assessed based on the sGA tool developed by the FIL (Merli, 2021). See Section 7.2 for details about sGA.

The study will enroll approximately 80 patients (approximately 40 patients in each cohort).

Based on the results from Cohort A and/ or B a protocol amendment will be considered to further evaluate the Lonca-R combination in these patient populations.

Enrolled patients in both cohorts will receive Lonca-R for 3 cycles. Patients who achieve CR after 3 cycles of Lonca-R treatment will continue to receive one additional cycle of Lonca-R. Patients who achieve PR after 3 cycles of Lonca-R will continue to receive additional 3 cycles of Lonca-R. Additionally, for Cohort B only, patients who achieve SD and derive clinical benefit per the treating physician may also continue to receive additional 3 cycles of Lonca-R. Details of dosing regimen are described in Section 6.3 (Table 4), (see Figure 2).

The duration of the study participation for each patient is defined as the time from the date of signed written informed consent to the completion of the follow-up period, withdrawal of consent, loss to follow-up, or death, whichever occurs first. Each patient enrolled in both cohorts will have the same duration of study participation.

18 weeks) or unacceptable toxicity, or other discontinuation criteria (see Section 5.5), whichever occurs first. Details of the treatment regimen are described in Table 4.

4.2.3 End of Treatment

An EoT visit should occur 28 (±7) days from the last dose of the study treatment, and in any case prior to the initiation of new anticancer treatment.

When EoT visit coincides with a scheduled visit, the scheduled visit will become EoT visit.

4.2.4 Follow-up Period

All patients, regardless of disease status, will be followed for up to 5 years from EoT, or until withdrawal of consent, loss to follow-up, or death, whichever occurs first. All patients will be followed every 12 weeks for 1 year, then every 24 weeks for up to 3 years then annually for up to 5 years from EoT.

When disease assessments are not planned for a follow-up visit, respective visit can be done by phone.

4.2.5 End of Study

The end of study (EoS) occurs at the last scheduled visit/procedure for the last patient, unless the study is terminated earlier by Sponsor. The date of death of individual patient is considered as EoS whose survival status was informed at any later contact date.

4.3 Steering Committee (SC)

A Steering Committee (SC) has been established for the study. It is composed of global DLBCL experts, who may participate in the study, and the Sponsor's representatives. The SC will collaborate with the Sponsor throughout the conduct of the trial by providing insights and recommendations towards successful study execution, assist with data interpretation, and advise if changes to the trial are warranted. More details can be found in the Steering Committee charter.

5 Patient Population

Patients must meet all inclusion criteria and none of the exclusion criteria to be eligible for the study. All criteria have to be assessed during screening, unless otherwise specified.

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

5.1 Inclusion Criteria

Inclusion Criteria for both cohorts:

1. Male or female
2. Pathologic diagnosis of DLBCL, as defined by the 2016 World Health Organization (WHO) classification (including patients with DLBCL transformed from indolent lymphoma), or high-grade B cell lymphoma (HGBCL), or Grade 3b follicular lymphoma (FL).
3. Measurable disease as defined by the 2014 Lugano Classification (Appendix 12.2).
4. Stages I-IV
5. Eastern Cooperative Oncology Group scale of performance status (ECOG PS) 0-2; ECOG PS 3 allowed if decline in status is deemed related to lymphoma & felt to be potentially reversible by the treating physician
6. Adequate organ function as defined by screening laboratory values within the following parameters:
   a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu L$ (off growth factors at least 72 hours)
   b. Platelet count $\geq 75 \times 10^3/\mu L$ without transfusion in the past 7 days
   c. Alanine aminotransferase (ALT), AST, and GGT $\leq 2.5 \times$ the upper limit of normal (ULN)
   d. Total bilirubin $\leq 1.5 \times$ ULN (patients with known Gilbert's syndrome may have a total bilirubin up to $\leq 3 \times$ ULN)
   e. Calculated creatinine clearance > 30 mL/min by the Cockcroft and Gault equation

   Note: A laboratory assessment may be repeated a maximum of two times during the screening period to confirm eligibility.
7. Women of childbearing potential (WOCBP)* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 12 months after the last dose of study treatment. Men with female partners who are of childbearing potential must agree to use a condom when sexually active or practice total abstinence from the time of the first dose until at least 7 months after the patient receives her/his last dose of study treatment

* WOCBP are defined as sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least one year. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Highly effective forms of birth control are methods that achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective forms of birth control include: hormonal contraceptives associated with inhibition of ovulation (oral, injectable, patch, and intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient.

Note: The double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only are not acceptable as highly effective methods of contraception.

Inclusion Criteria specific for Cohort A:

8. Unfit as defined by the sGA (includes all of the following):
    a. Aged ≥ 80 years
    b. ADL score of 6
    c. IADL score of 8
    d. CIRS-G: no score of 3-4 and < 5 scores of 2

Inclusion Criteria specific for Cohort B:

9. Frail as defined by the sGA:
    a. Aged ≥ 80 years
    b. ADL score of < 6 and/or
    c. IADL score of < 8 and/or
    d. CIRS-G: ≥ 1 score of 3-4 and/or ≥ 5 scores of 2

    OR

10. Aged ≥ 65 - < 80 with at least one of the following cardiac comorbidities that make anthracycline-containing regimens inadvisable as determined by the investigator
    a. Left ventricular ejection fraction (LVEF) ≥ 30 to < 50%
    b. History of myocardial infarction within 6 months prior to screening
    c. Ischemic heart disease

d. History of stroke within 12 months prior to screening

5.2 Exclusion Criteria

1. Known history of hypersensitivity to or positive serum human anti-drug antibody to a CD19 antibody
2. Previous therapy for DLBCL, HGBCL, or Grade 3b FL (with exception of corticosteroid course for symptom management of less than 14 days)
3. Previous therapy with loncastuximab tesirine and rituximab for any indication
4. Known history of hypersensitivity to any component of study treatment (loncastuximab tesirine and rituximab)
5. Human immunodeficiency virus (HIV) seropositive with any of the following:
   a. CD4+ T-cell (CD4+) counts < 350 cells/μL
   b. Acquired immunodeficiency syndrome (AIDS) – defining opportunistic infection within 12 months prior to screening
   c. Not on anti-retroviral therapy, or on anti-retroviral therapy for < 4 weeks at the time of screening
   d. HIV viral load ≥ 400 copies/mL
6. Serologic evidence of chronic hepatitis B virus (HBV) infection and unable or unwilling to receive standard prophylactic antiviral therapy or with detectable HBV viral load
7. Serologic evidence of hepatitis C virus (HCV) infection without completion of curative treatment or with detectable HCV viral load
8. History of Stevens-Johnson syndrome or toxic epidermal necrolysis
9. Lymphoma with active central nervous system involvement at the time of screening, including leptomeningeal disease
10. Clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath)
11. Major surgery, radiotherapy, chemotherapy, or other anti-neoplastic therapy within 14 days prior to start of study drug (Cycle 1 Day 1 [C1D1]), except shorter if approved by the Sponsor
12. Use of any other experimental medication within 14 days prior to start of study drug (C1D1)
13. Received live vaccine within 4 weeks of C1D1
14. Congenital long QT syndrome or a corrected QTcF interval of > 480 ms at screening (unless secondary to pacemaker or bundle branch block)
15. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that the Sponsor's Medical monitor and Investigator agree, and document should not be exclusionary

16. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk

5.3 Screening Failures

Patients who signed the ICF but were found not eligible for the study prior to receiving study drug are defined as screening failures.

For these patients, only limited information will be collected in the electronic case report form (eCRF):

- Informed consent
- Demographics
- Inclusion/exclusion criteria
- Serious adverse event (SAE) and/or death occurring during the Screening Period
- Screen Fail (documenting primary reason for screen failure)

5.4 Re-screening Procedures

A patient who did not meet the eligibility criteria, i.e., screening failure, may be considered for re-screening. Decision for re-screening must be confirmed by the Sponsor/Medical monitor. A re-screened patient will be assigned a new patient number. Patients who are rescreened are required to sign a new ICF.

5.5 Discontinuation

The reason for discontinuation, whether it is from study treatment or from study, and the date of discontinuation will be recorded for all patients in the eCRF.

Note: Once discontinued from the study for any reason, patients will not be permitted to be re-enrolled.

5.5.1 Discontinuation from Study Treatment

A patient may be discontinued from the study treatment for any of the following reasons:

- Adverse event
- Patient decision
- Investigator decision
- Major protocol deviation
- Lost to follow-up
- Disease progression (radiographic or clinical)
- Study termination by the Sponsor

- For Cohort A, patients who did not achieve a CR or PR after 3 cycles
- For Cohort B, patients who do not achieve a CR or PR or SD after 3 cycles
- Other

A patient with any of the following reasons will be immediately discontinued from study treatment:

- Pregnancy
- Death

IMPORTANT: Study treatment discontinuation is not equivalent to discontinuation from the study. Patients discontinuing the study treatment will be asked to perform an EoT visit (Section 4.2.3) and continue with the Follow-up period (Section 4.2.4) as per protocol.

The investigational site should make every effort to complete follow-up per protocol. If patients are unable to return to the site, patient status, including but not limited to survival status, may be obtained by site staff via phone, email, or mail.

5.5.2 Discontinuation from the Study

A patient may be discontinued from the study for any of the following reasons:

- Study completion
- Withdrawal of consent
- Investigator decision
- Lost to follow-up
- Study termination by the Sponsor
- Death
- Other

If a patient withdraws informed consent for study participation, no additional study data will be collected.

The Sponsor may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization. If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The study may be terminated at any time, for any reason, by the Sponsor. Patients still receiving study drug will have an EoT visit as described in Section 4.2.3 and schedule of events (SoE) (Table 2).

5.5.3 Lost to Follow-up

Patients who fail to return for protocol follow-up are to be contacted by the investigative site. Following a minimum of two documented unsuccessful telephone calls, the investigative site will send a registered letter to the patient in a final attempt to ensure protocol compliance.

5.5.4 Patient Replacements

No enrolled patients will be replaced.

6 Study Treatment

6.1 Study Drugs

Study drugs in this study will be loncastuximab tesirine and rituximab.

6.1.1 Loncastuximab Tesirine

Loncastuximab tesirine will be provided as a lyophilized white to off-white powder in single dose glass vials (10 mg loncastuximab tesirine per vial) and stored at 2°C to 8°C.

The lyophilized loncastuximab tesirine is formulated in 20 mM histidine, 175 mM sucrose, and 0.02% polysorbate 20, at pH 6.0. Prior to use, the study drug will be reconstituted with 2.2 mL of Sterile Water for Injection to deliver 2.0 mL at a concentration of 5 mg/mL, gently swirled (do not shake the vial) to ensure complete dissolution and homogeneity, and visually inspected. Sterile Water for Injection will be provided by study sites. Details of treatment regimen are described in Table 4.

Additional description of loncastuximab tesirine is included in the IB and pharmacy manual.

6.1.2 Rituximab

Rituximab is administered in an IV infusion on day 1 of each cycle. Use of the subcutaneous (s.c.) formulation (Cycle 2 and beyond) or biosimilars is allowed.

Refer to rituximab (or biosimilar) USPI for detailed information. Additional description is included in the pharmacy manual.

6.2 Management of Clinical Supplies

The investigator or designee must confirm appropriate temperature conditions have been maintained for study drugs received and any discrepancies are reported as instructed in the pharmacy manual.

Study drugs must be stored in a secure, monitored (manual or automated) area in accordance with the storage conditions specified in the pharmacy manual with access limited to authorized site staff.

The investigator or designee is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Detailed instructions regarding study drug shipment, handling, storage, preparation, administration, and final disposition of unused study treatment are included in the pharmacy manual.

6.2.1 Packaging and Storage

The study drugs will be supplied by the Sponsor through the designated packaging, labeling, and distribution center.

All study drugs must be stored according to the pharmacy manual, in a secure area.

The lyophilized formulation of loncastuximab tesirine must be stored refrigerated (2°C to 8°C) in original carton to protect from long-term exposure to light. Storage conditions of the study drugs will be described in pharmacy manual.

6.2.2 Preparation and Administration

The loncastuximab tesirine solution at the concentration of 5 mg/mL (see Section 6.1) will be the basis for the preparation of the infusion solution. The amount of the product to be diluted will depend on the dose level and the body weight of the patient. The weight of the patient at C1D1 can be used for calculating the dose. If the patient's weight measured on subsequent dosing days has changed by 10% or more compared to C1D1, then the dose must be recalculated.

Administration of loncastuximab tesirine will be performed by the Investigator or a qualified designee according to the pharmacy manual. Patients will receive an infusion of loncastuximab tesirine over 30 minutes on C1D2 and Day 1 of each following cycle. Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.

During cycles 2 and beyond, loncastuximab tesirine must be administered prior to rituximab and separated by 30 minutes (or more if clinically indicated; end time of loncastuximab tesirine administration used as reference).

Preparation and administration of rituximab will be according to the prescribing information and local practice.

Extravasation of intravenous (IV) study drugs may be associated with local irritation, swelling, pain, or tissue damage. The IV infusion site must be monitored for signs of IV infiltration or drug extravasation, and patients must be instructed to report immediately any signs of IV infiltration or drug extravasation during or after the infusion. Suspected extravasation of study drugs should be managed according to institutional protocol for management of extravasation of cytotoxic chemotherapy.

For patients who have a central line, administration of IV study drugs via this central line should be considered.

6.3 Study Treatment Assignment and Dosing

All patients enrolled will be assigned to Lonca-R. Details of the treatment given to the patients is described in Table 4.

During the Screening Period, patients may receive pre-phase therapy with prednisone 40 mg/m^2 for up to 14 days per the treating investigator's discretion.

Table 4 Treatment Regimens During the Course of the Study

Cohort	Treatment Regimen (1 cycle = 3 weeks [21 days])
Cohort A and cohort B	**Lonca-R**
	Cycle 1: Day 1: Rituximab IV 375 mg/m^2 Day 2: Loncastuximab tesirine 150 µg/kg IV **Cycle 2:** Day 1: Rituximab IV* 375 mg/m^2 and loncastuximab tesirine 150 µg/kg IV **Cycles 3-4:**† Day 1: Rituximab IV* 375 mg/m^2 and loncastuximab tesirine 75 µg/kg IV

Abbreviations: G-CSF, granulocyte colony-stimulating factor; IV, intravenous; Lonca-R, loncastuximab tesirine and rituximab.

*If subcutaneous rituximab is used, dose is 1400 mg flat dose

†Up to 6 total cycles of Lonca-R may be administered per protocol

Optional: G-CSF may be administered as primary prophylaxis starting with Cycle 1 of therapy and continue through each cycle of therapy for patients per the treating investigator's discretion and institution guidelines.

6.4 Premedication

Unless contraindicated, administer dexamethasone 4 mg orally or IV twice daily (BID) for 3 days, beginning the day before loncastuximab tesirine administration. If dexamethasone administration does not begin the day before loncastuximab tesirine administration, dexamethasone begins at least 2 hours prior to administration of loncastuximab tesirine administration.

Additional premedications may be given based on institutional practice for rituximab.

6.5 Treatment Compliance

Compliance will be verified by the study drug administration information recorded in the electronic data capture (EDC).

6.6 Definition and Management of Overdose

An overdose is any dose of study drug given to a patient that exceeds the maximum dose described in the protocol by 15% or more for loncastuximab tesirine. Any overdose, with or without associated AEs, must be promptly reported to the Sponsor (See Section 8.5.3). For loncastuximab tesirine, there are no data available to determine what the effects of overdose are and whether they can be reversed. For rituximab, the institutional guidelines are followed to manage overdose.

Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

6.7 Dose Delays and Modifications

6.7.1 Dose Delays and Modifications for Loncastuximab Tesirine

The criteria and guidance for dose delay and dose modifications of loncastuximab tesirine and rituximab in Lonca-R regimen are summarized in Table 5.

Table 5 Criteria for Dose Delay or Dose Modification of Loncastuximab Tesirine or Rituximab in Lonca-R regimen

Toxicity	Loncastuximab Tesirine	Rituximab
Grade ≥3 non-hematologic adverse events	• Withhold until the toxicity resolves to Grade ≤ 1, (Grade 1 or baseline for peripheral neuropathy) • If dosing is delayed by more than 3 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, then subsequent doses must be reduced by 50%. If the toxicity recurs following dose reduction, consider discontinuation • Note: Patients who have a toxicity meeting the criteria for dose reduction following Cycle 2 will receive the protocol-specified dose of 75 µg/kg for Cycle 3, i.e., they will not have an additional dose reduction for Cycle 3.	• Hold until the toxicity resolves to Grade ≤ 1, (Grade 1 or baseline for peripheral neuropathy)
Grade ≥2 edema, effusion	• Withhold until the toxicity resolves to Grade ≤ 1 • If dosing is delayed by more than 3 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, then subsequent doses must be reduced by 50%. If the toxicity recurs following dose reduction, consider discontinuation. • Note: Patients who have a toxicity meeting the criteria for dose reduction following Cycle 2 will receive the protocol-specified dose of 75 µg/kg for Cycle 3, i.e., they will not have an additional dose reduction for Cycle 3.	• Hold until the toxicity resolves to Grade ≤ 1
Grade ≥3 neutropenia or thrombocytopenia	• Withhold until toxicity resolves to Grade ≤ 2 • If dosing is delayed by more than 3 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, then subsequent doses must be reduced by 50%. If the toxicity reoccurs following dose reduction, consider discontinuation. • Note: Patients who have a toxicity meeting the criteria for dose reduction following Cycle 2 will receive the protocol-specified dose of 75 µg/kg for Cycle 3, i.e., they will not have an additional dose reduction for Cycle 3.	• Hold until toxicity resolves to Grade ≤ 2

6.8 Supportive Care

6.8.1 Management of Edema and Pleural Effusion

In patients treated with loncastuximab tesirine, spironolactone at standard doses should be administered for patients with weight gain greater than 1 kg from C1D1, new or worsening edema, and/or new or worsening pleural effusion. The dose of spironolactone may be titrated as clinically indicated. Additional diuretic support may be added if there is further increase in weight, edema, or pleural effusion. Additionally, patients should be advised to monitor their weight on a daily basis, at around the same time (preferably in the morning), and to notify the study site if they gain >1 kg (2.2 pounds) over baseline.

6.8.2 Prevention and Management of Infusion-Related Hypersensitivity Reactions

Medications for the treatment of severe hypersensitivity reactions, including anaphylaxis, must be available for immediate use and may be administered according to site standard treatment protocols.

Any patient who experiences a Grade ≥ 2 infusion-related hypersensitivity reaction will receive prophylactic treatment in subsequent cycles according to institutional guidelines.

6.8.3 Prevention and Management of Skin Toxicity

Skin toxicity has been reported in patients receiving loncastuximab tesirine for hematologic malignancies. Often, the toxicities manifested as rash were reported in sun exposed areas; it is therefore recommended that precautions are taken to avoid exposure of skin to sunlight, even through glass (e.g., use of sun protective clothing and sunglasses, sunscreen with a sun protection factor ≥ 30 applied every 2 hours). Also, fragrance-free detergents and soaps are recommended.

Treatment recommendations for skin toxicities include topical treatment to affected areas:

- Maculopapular rash or photosensitivity rash: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%).
- Pruritus: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider oral antipruritic.
- Xerosis or hyperpigmentation: consider ammonium lactate 12% or urea 20% BID; and triamcinolone 0.1% and triamcinolone 0.1% cream BID.
- Blistering rash: silvadene 1% cream BID and consider laboratory testing for blistering disorder (Varicella Zoster Virus /Herpes Simplex Virus and bacterial infection; bullous pemphigoid; pemphigus).

Systemic corticosteroid therapy should be considered for giving to patients who develop clinically significant skin toxicity. Also, for Grade ≥2 skin toxicities consider a dermatology consult.

6.8.4 Prevention of Tumor Lysis Syndrome

Patients are observed for development of tumor lysis syndrome (TLS). The risk of TLS will be assessed by the Investigator and prophylaxis and management undertaken per institutional guidelines prior to the initiation of the first study drug. TLS related laboratory tests in patients with intermediate or high risk, will be checked daily during first 24-72 hours after C1D1 or according to institutional routine (Table 2). Prophylaxis may include but not be limited to the following:

- Appropriate hydration
- Administration of an agent to reduce uric acid, if indicated
- Hospitalization for high risk patients, if indicated

6.8.5 Prevention of Febrile Neutropenia

G-CSF may be administered as primary prophylaxis starting with Cycle 1 of therapy and continue through each cycle of therapy for patients per the treating investigator's discretion and institutional guidelines.

6.8.6 Prevention of Infection

Anti-infectious prophylaxis (including opportunistic infections) can be given as per institutional guidelines.

6.8.7 Other Supportive Care

Patients who show evidence of prior hepatitis B infection (Hepatitis B surface antigen [HbsAg] positive [regardless of antibody status] or HbsAg negative but hepatitis B core antibody-positive) receive prophylactic antiviral therapy and be monitored for hepatitis B reactivation according to institutional guidelines.

As testing in animals showed testicular toxicity (atrophy with reduced spermatogenesis), male patients are advised to consider cryopreservation of sperm prior to treatment with loncastuximab tesirine, where applicable.

6.9 Concomitant Medications and Procedures

Medications (except for the study drug) and procedures will be recorded in the eCRF starting from the ICF signature date or from 14 days prior to C1D1, whichever is earlier, and continuing until at least 30 days after last dose of study treatment and as indicated for AE/SAEs thereafter.

6.9.1 Permitted During Study

Medications or procedures for the clinical care of the patient, including management of AEs, are permitted during the study, except for those listed in Section 6.9.2.

6.9.2 Prohibited During Study

The following treatments are prohibited during study treatment but are allowed in the follow-up period.

- Other anticancer therapy with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer
- Other investigational agents
- Live vaccines until 3 months after last dose of study drug
- Refer to USPI of rituximab (or biosimilar) for prohibited treatments

7 Study Assessments and Procedures

Study assessments and procedures are to be completed as described below; however, there may be situations (e.g., safety issues) preventing their completion. In such case, the Investigator takes all actions necessary to ensure the safety and well-being of the patient and document the reason for not performing the assessment.

7.1 Informed Consent

Informed consent, as documented by a signed and dated ICF, must be obtained prior to performing any study procedures. Results (e.g., from laboratory tests or radiographic evaluations, etc.) obtained prior to the date of informed consent but within the allowed timeframe may be used for determination of patient eligibility only if obtained as part of standard care. For additional details, please refer to Section 10.3.

7.2 Demographics and Baseline Characteristics

These assessments include:

- Demographic information such as age, gender, ethnicity, and race; to the extent allowed by local regulations.
- Cancer medical history, which includes a complete history of all surgeries and significant diagnoses, and all cancer treatment, including surgery, radiation therapy, chemotherapy, etc.
- Any other relevant medical history.
- Collection of information on prior medications used from ICF signature date or at least within 14 days prior to C1D1, whichever is earlier.
- Simplified geriatric assessment (sGA, Section 1.1): sGA is to be completed for patients aged ≥80 years old. It is based on the scores of 3 surveys: ADL (Appendix 12.4), IADL (Appendix 12.5) and CIRS-G (Appendix 12.6) and will be used for this study to determine whether a patient is unfit or frail according to Inclusion Criteria 8 and 9 (Section 5.1), respectively. sGA should be performed by the Investigator (or delegate) and done at the end of the screening period once all other eligibility criteria have been met.

7.3 Efficacy Assessments

Disease assessments will occur as per SoE (Table 2) until progression.

Imaging and clinical examination for lymphoma will be performed at all disease assessment time points.

Positron emission tomography-computed tomography (PET-CT) of the neck/chest/abdomen/pelvis and other areas of known disease or newly suspected disease, as well as a clinical examination for lymphoma, will be performed. If it is known that the tumor is fluorodeoxyglucose (FDG)-avid, the baseline CT as part of the PET-CT does not have to be

performed with contrast medium; however, if the baseline PET-CT shows that the tumor is not FDG-avid, diagnostic CT with IV contrast will need to be obtained as a baseline examination. For this reason, if it is known that the tumor is not FDG-avid on previous imaging, consideration should be given to obtaining a diagnostic quality CT with IV contrast as part of the initial PET-CT examination. Patients who have a contraindication to CT IV contrast medium have magnetic resonance imaging (MRI) examinations performed instead. The assessment method determined to identify sites of disease at Baseline (i.e., PET-CT, CT, MRI) is used for all subsequent assessments.

Patients whose tumor is not FDG-avid have a bone marrow biopsy as part of their baseline staging and disease assessment if clinically appropriate.

Screening (Baseline) imaging must be performed within 4 weeks prior to C1D1.

During the treatment period, imaging will be performed prior to Cycle 4 and at the end of Cycle 6 (as applicable). Imaging prior to Cycle 4 and at end of Cycle 6 should be performed within ±1 weeks of the scheduled time point; all other imaging will be performed within ±2 weeks of the scheduled time point.

During the follow-up period, patients who discontinued study drug for reasons other than disease progression or initiation of (an)other anti-cancer therapy(ies) will have imaging performed every 12 (± 2) weeks until 1 year from EoT, then every 24 weeks up to 2 years, then annually up to 5 years from EoT.

If imaging has been performed within 6 weeks of EoT, it does not need to be repeated at EoT visit. Additional disease assessments may be obtained, if clinically indicated.

The patient's response to treatment will be determined according to the 2014 Lugano Classification Criteria (Appendix 12.2) as CR, PR, SD, or progressive disease (PD). Upon indication of clinical progression (nonradiographic), a radiographic disease assessment to confirm the PD is expected, if clinically indicated, in order to ensure appropriate data collection toward the primary endpoint of this protocol.

Images will be obtained according to local site imaging requirements.

7.4 Safety Assessments

Safety will be assessed based on the procedures in the subsection below. AEs/SAEs collection and reporting is described in Section 8.

Unless otherwise specified, all safety assessments on dosing days will be done prior to study drug administration. Additional safety assessments may be performed by the Investigator when clinically indicated.

7.4.1 Physical Examination

Planned time points for physical examination are provided in the SoE (Table 2). Physical examination will be performed according to institutional standards.

7.4.2 ECOG Performance Status

ECOG PS grades are presented in Appendix 12.1 and will be captured at the planned time points provided in the SoE (Table 2).

7.4.3 Height and Weight

Planned time points for height and weight are provided in the SoE (Table 2). Additional measurements will be performed if clinically indicated.

Patients are advised to monitor their weight at home to mitigate the risks for edema/effusions. Refer to Section 6.8 for further details.

7.4.4 Vital Signs

Planned time points for vital signs are provided in the SoE (Table 2). Vital signs include the measurements of arterial blood pressure (systolic and diastolic), heart rate, respiratory rate, and body temperature and will be performed according to the institutional standards.

For Day 1 of each cycle and C1D2, vital signs are to be measured before the start of the study drug infusion and at the end of infusion.

7.4.5 Laboratory Tests

Samples will be collected at the time points specified as per SoE (Table 2).

Additional sample(s) may be collected and analyzed if clinically indicated. The C1D1 laboratory tests do not need to be repeated if the laboratory tests for eligibility were done within 3 days of C1D1.

Hematology: White blood cells (WBC) with 5-part differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, hemoglobin, and hematocrit.

Chemistry: ALT, AST, GGT, alkaline phosphatase, amylase, lipase, total bilirubin (conjugated and unconjugated bilirubin only when total bilirubin is abnormal), sodium, potassium, chloride, phosphate, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, creatinine, creatine phosphokinase, total protein, albumin, glucose, and lactate dehydrogenase.

Urinalysis: pH, specific gravity, protein, WBC, red blood cell (RBC), ketones, glucose, and bilirubin.

Urinalysis may be performed by dipstick. Abnormal findings will be followed up with a microscopic evaluation and/or additional assessments as clinically indicated. A microscopic evaluation consists at a minimum of WBC and RBC quantitation per high power field, as well as semi-quantitative assessment of other cells and substances, if present, such as epithelial cells, bacteria, and crystals ("few," "moderate," "many"). Other evaluations depending on microscopic findings may be added.

Viral detection: HBV and/or HCV serology tests, and viral load test if clinically indicated.

HIV serology tests, and HIV viral load and /or CD4+ T cell count if clinically indicated.

7.4.6 Pregnancy Test

A highly sensitive human chorionic gonadotropin (β-HCG) test in urine or blood β-HCG test will be performed in females of childbearing potential for eligibility (see Section 5.1) and throughout the study as per SoE (Table 2).

After starting the study, additional pregnancy testing will be performed according to the SoEs (Table 2) and as needed.

Pregnancy test will not be required for females who are post-menopausal or those with prior hysterectomy.

If a pregnancy test is positive, the study drug must be held pending till confirmation. If the pregnancy is confirmed, study treatment will be discontinued permanently for the patient. Refer to Section 8.5.2 for the handling of the patient and reporting the event.

7.4.7 Electrocardiograms

One 12-lead electrocardiogram (ECG) will be performed at screening as per SoE (Table 2). The ECG will be performed after the patient is resting for at least 5 minutes. Additional ECG assessments may be performed as clinically indicated.

Assessments will include determination of heart rate and rhythm and the PR, QRS, QT, and QTcF intervals.

7.5 Pharmacokinetics, CCI , and Immunogenicity

Pharmacokinetic, ADA, CCI samples will be collected as per SoE (Table 2). Additional biological samples may be collected by the Investigator when clinically indicated (e.g., at the time of significant AEs that are at least possibly related to the study drug) and may be used for PK CCI .

When multiple samples are required at the same time point, collection of safety samples should be first followed by PK, then ADA, CCI .

In order to better understand the disease, metabolic disposition, and pharmacologic behavior of loncastuximab tesirine in humans, samples remaining after primary analyses may be utilized for further analyses.

Biological samples may be retained for up to 10 years to further address scientific questions as new information in regards to the disease or the study drug becomes available.

For detailed instructions related to central laboratory sample collection, labelling, processing, storage, or shipment, refer to the appropriate laboratory manual(s).

7.5.1 Pharmacokinetic Assessment

The concentration in serum of loncastuximab tesirine PBD-conjugated antibody, total antibody and SG3199 unconjugated warhead will be assessed by a central laboratory designated by the Sponsor using validated bioanalytical methods.

Approximately 6 mL of whole blood will be collected as per SoE (Table 2). The predose PK samples will be collected preferably within 2 hours prior to start of infusion and at the end

(within -5 to +10 min) of Lonca infusion. Blood should be drawn from a vein away from the one used for study drug infusion.

Pharmacokinetic samples must be stored at -70°C. Please refer to the laboratory manual for detailed instructions regarding specimen handling and shipment.

7.5.2 Immunogenicity

Detection of ADAs will be performed by using a screening assay for identification of antibody positive samples/patients, a confirmation assay, and titer assessment, and will be performed using the Meso-Scale Discovery Electrochemiluminescence platform. If an ADA is confirmed, as appropriate, a functional assay for the assessment of the neutralizing capacity of the ADA will be performed.

Approximately 6 mL of whole blood will be collected as per SoE (Table 2). Blood should be drawn from a vein away from the one used for study drug infusion.

For patients who test positive for ADAs, an additional ADA sample may be requested for testing every 12 weeks following the EOT visit until the ADA titer falls to a background level.

ADA samples must be stored at -70°C. Please refer to the laboratory manual for detailed instructions regarding specimen handling and shipment.

7.5.3 CCI

7.5.3.1 CCI

CCI

7.5.3.2 CCI

CCI

7.6 Patient Reported Outcomes

Patient reported outcomes will be administered as per SoE (Table 2).

The impact of loncastuximab tesirine treatment on disease- and treatment-related symptoms, as well as various aspects of patient's health-related quality of life will be assessed by the following instrument:

- Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)

Responses from patients will be captured via paper questionnaires.

All questionnaires will be completed in the respondent's native language, at the scheduled study visit prior to the patient seeing the investigator for any clinical assessment or treatment. Patients will provide responses at the study site. The patient will be given enough instructions, space, time and privacy to complete the questionnaires by themselves and without any assistance from anyone else. The study coordinator encourages the patient to complete the questionnaire without any missing responses.

While completing the questionnaire, some respondents might ask questions indicating they are having difficulty reading the PRO questionnaires. For example, a respondent may ask the meaning of specific items or response options so that he/she can better understand and respond. If this occurs, an interviewer may assist the respondent by re-reading the question or response options for him/her verbatim. If the respondent asks the interviewer to interpret the meaning of an item or response options, no explanation or interpretation will be offered but suggest that the subject use his/her own interpretation of the question and response options. Respondents answer the questions based on what they think the questions mean.

If a respondent is having difficulty with the response choices (for example, he or she may say "I don't know" or something different than what is stated on the questionnaire), it is important to direct the respondent to pick the response that best fit how he/she feels. The respondent must not record a response that is not one of the provided response options for each question (e.g., respondent does not write in his/her own response). The interviewer may re-read the response choices verbatim; however, do not rephrase the response choices or try to simplify the language.

FACT-Lym

FACT-Lym (see Appendix 12.3) is a lymphoma-specific subscale for the Functional Assessment of Cancer Therapy (FACT) questionnaire (Hlubocky et al., 2013). It consists of 15 specific items that are used together with the core 27-item questionnaire FACT-G. 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. A higher score indicates a worse level of QoL.

8 Adverse Events Reporting

Reporting of AEs to competent authorities and Independent Review Boards (IRBs)/Independent Ethics Committees (IECs) will be consistent with current laws, regulations, and guidelines.

8.1 Definition of Adverse Events and Serious Adverse Events

8.1.1 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.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

Test results collected during the study (e.g., laboratory values, physical examination, ECGs, etc.) or identified from review of other documents may constitute AEs if deemed clinically significant.

8.1.2 Serious Adverse Events

An SAE is defined as any AE that:

- results in death.
- is life threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.).
- requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization for elective procedures or for protocol compliance is not considered an SAE).
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- important medical events that do not meet the preceding criteria but based on appropriate medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated pharmaceutical product will be considered a medically important event and subject to expedited reporting requirements.

8.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities/other abnormal assessments that require medical or surgical intervention or lead to pharmaceutical product interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. If the laboratory abnormality/other abnormal assessment is consistent with a clinical diagnosis, report the AE using the diagnosis (i.e., anemia), not the laboratory result (i.e., decreased hemoglobin).

8.2 Eliciting and Reporting Adverse Events/Serious Adverse Events

Patients will be instructed to contact the Investigator at any time after ICF signature if any symptoms develop. At each study visit, patients will be asked a nonleading question to elicit any medically related changes in their well-being. Patients may also report AEs voluntarily and they will be instructed to contact the Investigator between visits if any symptoms develop or worsen.

AEs will be reported starting when the patient provides written informed consent. Clinically significant medical conditions present at the time of ICF signature will be reported as medical history. Clinically significant medical conditions that start or worsen after ICF signature will be reported as AEs.

All AE/SAEs regardless of relationship to study drug, will be reported from the time the patient signs the ICF until 15 weeks after the last dose of study drug or the start of new anti-cancer therapy, whichever is earlier; thereafter only related SAEs will be reported.

Whenever possible, AEs should be reported as a diagnosis rather than individual signs and symptoms. If no diagnosis is available or has been identified, then the primary symptom is reported.

In general, the term ‘disease progression’ should not be used for reporting an AE/SAE. However, AEs/SAEs that are complications of disease progression should be reported.

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected will include event term, date of onset, assessment of severity (Section 8.3), seriousness (Section 8.1), relationship to study drug (Section 8.4), action taken with study drug, date of resolution of the event or ongoing (when no resolution by the end of the reporting period), any required treatment or evaluations, and outcome.

New SAEs and any recurrent episodes, progression, or complications of the original SAE must be reported to the drug safety department of the Sponsor or delegate (e.g., contract research organization [CRO]) within 24 hours after the time site personnel first learn about the event. Reporting will occur through the EDC system.

8.3 Assessment of Severity

The AEs will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. For events not included in the CTCAE criteria, the severity of the AE is graded on a scale of 1 to 5 as shown in Table 6.

Table 6 Definition of Severity Grades for CTCAE

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

[a] ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The AEs characterized as intermittent do not require documentation of onset and duration of each episode.

8.4 Assessment of Causality

The Investigator's assessment of an AE's relationship to study drug is an important part of safety reporting, but is not a factor in determining whether an AE is reported. An AE will be assessed as related to study drug if there is a reasonable possibility of causal relationship with the use of the study drug. For SAEs, whenever possible, the Investigator should provide a rationale for the causality assessment.

The investigator or qualified subinvestigator is responsible for providing an assessment of the relationship to the study drug(s) using clinical judgment and the following considerations:

Causality	Definition
Not related	An adverse event is not related to the study drug
Unlikely related	An adverse event where evidence exists for an alternative explanation other than the study drug e.g., concomitant medication(s), concomitant disease(s), or time to onset suggests unlikely relationship.
Possibly related	An adverse event that might be due to study drug. An alternative explanation (e.g., concomitant medication(s), concomitant disease(s), or time to onset) is inconclusive, where a causal relationship with study drug cannot be ruled out.
Probably related	An adverse event that might be due to study drug. An alternative explanation (e.g., concomitant medication(s), concomitant disease(s)) is less likely, and where a causal relationship with study drug is more suggestive (i.e., time to onset, positive dechallenge/rechallenge).
Related	An adverse event where an alternative explanation cannot be explained and, therefore, considered related to study drug.

8.5 Special Situations Reports

8.5.1 Definitions of Special Situations

Any special situation occurring in a participant that may require expedited reporting or safety review may include the following with the study drug:

- Pregnancy reports (see Section 8.5.2)
- Overdose reports (see Section 8.5.3)
- Other special situations (see Section 8.5.4), such as:
    - Suspected misuse or abuse
    - Accidental exposure
    - Medication error
    - Exposure to the study drug from breast-feeding
    - Adverse events associated with product complaints
    - Suspected transmission of an infectious agent via a medicinal product, which will be classified as an SAE

8.5.2 Reporting Pregnancy

Any pregnancy in a patient that occurs from signing the ICF up to 12 months after last dose of study treatment must be reported using the Pregnancy Report Form. Any pregnancy in a partner of a male participant that occurs from signing the ICF up to 7 months after last dose of study treatment must be reported.

Pregnancy must be reported within 24 hours after the site personnel first learn of the pregnancy. The pregnancy itself is not considered an AE. However, the pregnancy must be followed to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient discontinued from the study. Abortions (elective or spontaneous) occurring during the pregnancy reporting period must be reported as an SAE.

Any SAE occurring in association with a pregnancy that is brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study drug must be promptly reported in the same manner.

Once pregnancy is confirmed in a study participant, study drug will be discontinued, see Section 7.4.6 for additional information.

8.5.3 Reporting Overdose

An overdose of the study drug(s) is defined under Section 6.6.

An overdose itself is not considered an AE. However, if such an overdose occurs during the study, with or without any signs or symptoms, it must be reported to drug safety department of the Sponsor or delegate (e.g., CRO) within 24 hours after the time site personnel first learn about the event.

8.5.4 Reporting Other Special Situations

All other special situation reports must be reported to drug safety department of the Sponsor or delegate (e.g., CRO) within 24 hours after the time site personnel first become aware of the situation.

8.6 Data Monitoring Committee

A data monitoring committee (DMC) will primarily review the collection of AEs and other safety-related information on a periodic basis to ensure the safety of patients enrolled in this study. They will provide expertise and make recommendations, based on independent evaluation, on study conduct and progress, which concern the continuation, modification, or termination of the study. The DMC will be composed of at least one clinician with lymphoma expertise and a biostatistician.

Details regarding the DMC responsibilities, authorities, and procedures will be included in a separate and mutually agreed DMC charter.

9 Statistical Considerations

Full details of the analysis plan, including a more technical and detailed elaboration of the statistical analyses will be provided in the statistical analysis plan (SAP). The SAP will be developed and finalized before database lock.

9.1 Sample Size Determination

A sample size of 40 patients for each cohort is considered adequate to assess safety and efficacy in the corresponding study population. Table 7 lists estimated CR rate and the corresponding 95% exact CIs by number of responders from a sample size of 40 patients.

Table 7 Estimated Complete Response Rate and 95% CI for each cohort

Number of Patients	Number of Responders	CRR	95% CI for CRR (Exact)
40	12	30%	(16.6, 46.5)
40	16	40%	(24.9, 56.7)
40	20	50%	(33.8, 66.2)
40	24	60%	(43.3, 75.1)

Abbreviations: CI, confidence interval; CRR, complete response rate; ORR, overall response rate.

9.2 Analysis Populations

- All-Treated Population: All patients who receive at least 1 dose of study drug. This population will be used in the primary analyses of efficacy and safety for both cohorts.
- Patient-reported Outcomes Population: All patients who receive at least one dose of study treatment and complete at least one questionnaire at baseline and at one post baseline visit.
- The PK Population: All patients who receive study drug and have at least 1 pre- and 1 post-dose valid PK assessment.
- The Immunogenicity Population: All patients who receive study drug and have at least 1 valid anti-drug antibody assessment.
- CCI [redacted]

9.3 Interim Analysis

No formal interim analysis is planned.

9.4 Final Analysis

All efficacy and safety endpoints will be analyzed and reported in the clinical study report (CSR).

9.5 Demographics and Baseline Characteristics

Demographics and Baseline characteristics, such as cancer history and medications history, will be summarized for the All-treated Population (Cohort A and Cohort B).

9.6 Exposure to Treatments

Exposure to study drug, prior, and concomitant medications will be summarized for the All-Treated Population by dose level. Dose interruptions, reductions, and relative dose intensity will also be summarized.

9.7 Efficacy Analyses

Primary efficacy analyses will be based on response as determined by treating investigator.

9.7.1 Complete Response Rate

The CR rate will be defined as the proportion of patients with a best overall response (BOR) of CR, based on response assessments obtained on or prior to the start of subsequent cancer treatment. The percentage of CR rate with its 95% CI will be presented. For the primary CR rate analysis, patients with missing response or not evaluable information will be counted as failures. Further details will be provided in the SAP.

9.7.2 Overall Response Rate

The ORR will be defined as the proportion of patients with a BOR of CR or PR. The overall response category will be derived based on response assessment performed on or before the start of subsequent anti-cancer therapy. For the primary ORR, patients with a CR or PR will be counted as successes and all other patients (including those with missing response information) will be counted as failures.

The ORR with its 95% CI will be presented. In contrast to CR, PR, or PD, a BOR of SD can only be made after the patient is on-study for a minimum of 35 days after the first dose of study drug (Cohort A and Cohort B). Any tumor assessment indicating SD before this time period will be considered as a non-evaluable for BOR if no assessment after this time period is available.

9.7.3 Duration of Response

The DoR will be defined among responders (CR or PR) as the time from the earliest date of first response until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression based on investigator assessment. For patients who have not progressed or died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment on or prior to initiation of a new anticancer therapy. A sensitivity analysis of DoR is planned to be conducted in which the DoR for patients undergoing sacrococcygeal teratoma (SCT) is not censored at the last evaluable disease assessment prior to SCT. The data will be analyzed by

the Kaplan-Meier method. The median DoR and 95% CI will be presented. Further details will be provided in the SAP.

9.7.4 2-year Progression-free Survival

The PFS will be defined among All-treated patients as the time from first dose of study drug until the first date of either disease progression or death due to any cause.

The date of disease progression will be defined as the earliest date of disease progression based on investigator assessment. For patients whose disease has not progressed at the time of the analysis, censoring will be performed using the date of the last valid disease assessment on or prior to initiation of a new anticancer therapy. 2-yr PFS is defined as the proportion of patients that are PFS event-free at 2 years per investigator assessment. 2-yr PFS along with 95% CI will be estimated using Kaplan-Meier method. Further details will be provided in the SAP.

9.7.5 3-year Overall Survival

The OS will be defined as the time from randomization date until death due to any cause.

For patients who have not died at the time of the analysis, censoring will be performed using the date the patient was last known to be alive. The 3-year OS is defined as the proportion of patients that are OS event-free at 3 years. 3-year OS along with 95% CI will be estimated using Kaplan-Meier method. Further details will be provided in the SAP.

9.8 Safety Analyses

Safety analyses will be presented descriptively.

9.8.1 Adverse Events

The focus of AE summarization will be on TEAEs. A TEAE is defined as an AE that occurs or worsens in the period extending from the first dose of study drug to 15 weeks after the last dose of study drug in this study or the start of a new anticancer therapy, whichever is earlier.

All TEAEs will be summarized. Summary tables will be presented to show the number of patients reporting TEAEs by severity grade and corresponding percentages. A patient who reports multiple TEAEs within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade.

Separate summaries will be prepared for TEAEs classified as severe or life-threatening (≥ Grade 3); study drug-related AEs; AEs leading to treatment interruption, modification, or discontinuation; AEs of special interest; SAEs; and death.

9.8.2 Clinical Laboratory Results

Clinical hematology, biochemistry, and urinalysis data will be summarized at each scheduled assessment. Shifts for clinical laboratory results that can be graded according to CTCAE v5.0 (or more recent) will be summarized by CTCAE grade. Shifts for other numeric laboratory results will be by high/normal/low flag. Shifts for all other laboratory results will be by normal/abnormal flag.

Summaries by visit will include data from scheduled assessments, and all data will be reported according to the nominal visit date for which it was recorded. Unscheduled data will be included in "worst-case post-Baseline" summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study drug. Further details will be provided in the SAP.

9.8.3 Additional Safety Assessments

The results of scheduled assessments of vital signs, physical examinations, ECOG performance status, and 12-lead ECGs will be summarized. All data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in "worst case" summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study drug. All data will be listed. Further details will be provided in the SAP.

9.9 Pharmacokinetic Analysis

For the PK-evaluable patients, PK parameters will be determined for the typical patient and estimated for individual patients using a population PK analysis method. Analysis will consider model development for conjugated antibodies (Ab) and total Ab. If supported by available data, the model may also include characterization of SG3199 unconjugated measures. Intrinsic and extrinsic factors which may have influence on PK parameter variability will be tested and assessed for inclusion in the final model. Demographic data for the PK population will be summarized. Potential correlations of PK parameters to safety and efficacy endpoints, as appropriate, may be evaluated. Results of the population PK analysis will be reported separately.

9.10 Immunogenicity Analysis

Anti-drug antibody will be measured for Lonca-R arm during the study using screening and confirmatory assays with titer evaluation (Figure 3).

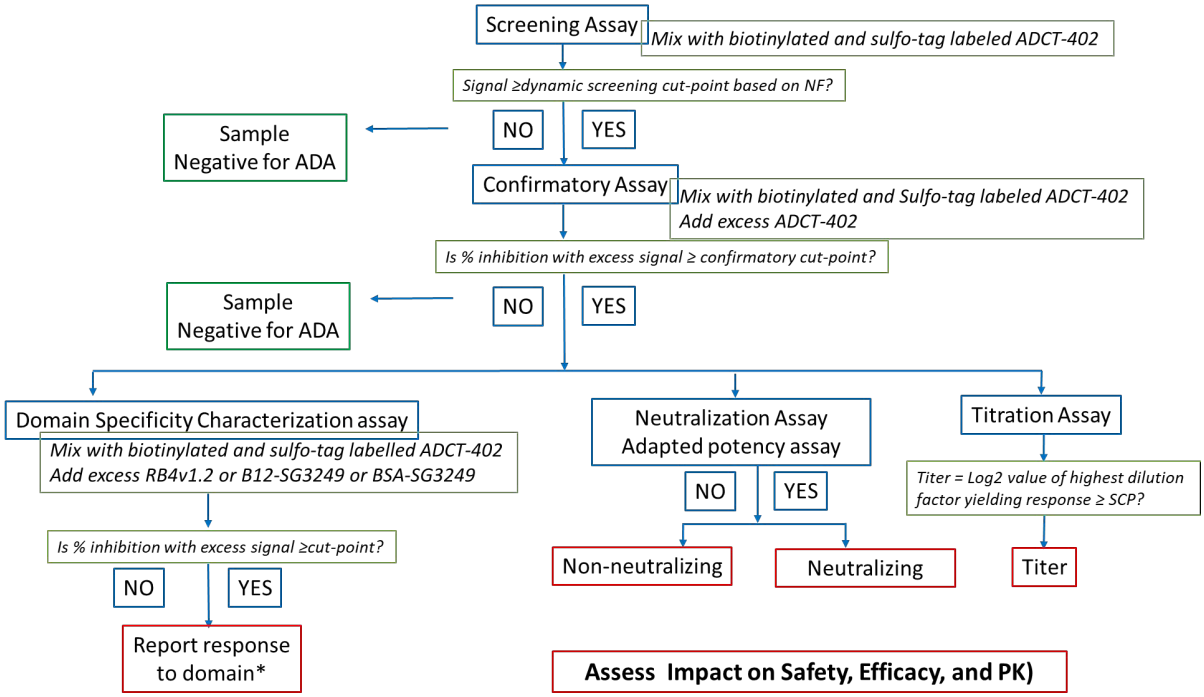

Figure 3 Anti-drug Antibody Tiered Immunogenicity Testing Strategy

Abbreviations: ADA, anti-drug antibody; ADCT-402, loncastuximab tesirine; BSA-SG3249, bovine serum albumin conjugated to SG3249; Intermediate monoclonal antibody RB4v1.2; irrelevant monoclonal antibody B12 based ADC B12-SG3249; NF, normalization factor; PK, pharmacokinetics; SCP, screening cut-point.

Results from ADA testing will include tabular summarization for number/proportion of patients with confirmed positive predose ADA response, confirmed number of patients with postdose ADA response only, confirmed number of patients with positive ADA response at any time, and confirmed positive ADA before and after dose. The denominator will be the total number of patients tested for ADAs in the study.

9.11 Subgroup Analyses

Subgroup analyses will be performed for ORR, DoR, CRR, 2-year PFS, and 3-year OS and safety endpoints using the following variables if appropriate.

- Demographic variables:
  - age group (Cohort B only)
    - age 65-79
    - ≥80
  - gender
  - race
  - ECOG Performance Status
    - 0-1
    - 2-3
  - region (North America vs rest of world)

- Baseline disease characteristics:
  - tumor staging
    - I-II
    - III-IV
  - Cell of origin
    - Germinal center B-cell (GCB)
    - Non-GCB
  - International Prognostic Index (IPI)
    - 0-2
    - 3-5
  - Lactate dehydrogenase
    - Normal
    - Elevated
  - Albumin
    - ≤3.5 g/dL
    - ≥3.5 g/dL
  - Extranodal involvement
    - Yes
    - No
  - Bulky disease
    - ≥10 cm
    - <10 cm
  - Histology
    - DLBCL, NOS
    - HGBCL
    - Transformed iNHL
    - FL 3b
- Pre-Phase Therapy
  - Yes
  - No
- The proportion of patients achieving a CR after 3 cycles vs 6 cycles as follows:
  - Cohort A Lonca-R
  - Cohort B Lonca-R

Other subgroup analysis factors may be evaluated as appropriate and the details will be provided in SAP.

9.12 Patient-reported Outcomes

Patient-reported outcomes will be analyzed among PRO population. Details will be provided in the SAP.

9.13 CCI

CCI

10 Regulatory, Ethical, and Study Oversight/Management Considerations

10.1 Regulatory and Ethical Considerations

The study will be performed in accordance with the protocol and with the Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to applicable laws and regulations.

Study information from this protocol will be posted on publicly available clinical study registries before enrollment of patients begins.

10.2 Financial Disclosure and Obligations

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.3 Patient Information and Consent

The investigator or his/her representative will explain the nature of the study to the participant or his/her LAR and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their LAR will be required to sign a statement of informed consent that meets the requirements of any applicable regulations, guidelines, and the IRB/IEC or study center.

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

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study, unless otherwise indicated by the IRB/IEC (local or global, as applicable). In such cases, the reason for not re-consenting the patient will be documented.

A copy of the ICF(s) must be provided to the participant his/her LAR.

Separate ICF(s) or a separate section in the main ICF may be added to allow the possibility to perform optional exploratory research, such as the use of remaining mandatory samples for future research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason. A separate signature will be required to document a participant's agreement to such optional research. Participants who decline to participate in this optional research will not provide this separate signature

10.4 Data Protection

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

Sponsor maintains organizational and security measures (e.g., pseudonymisation, data protection policy, backups, network security, physical access control, monitoring network activity) to safeguard patient’s personal data that are transferred to Sponsor from loss, misuse, unauthorized access, disclosure, alteration or destruction and, when required, will cause third parties accessing your Personal Data to maintain the same and to assist Sponsor in complying with its obligations under applicable laws regarding personal data protection.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.5 Data Quality Assurance

Study personnel involved in conducting this study will be qualified by education training and experience to perform their respective tasks.

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., central laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

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

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Upon completion of the study, the Sponsor shall prepare a summary of the study outcome in accordance with the ICH E3 guidelines for submission to the appropriate regulatory authority(ies).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.6 Source Documents

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

Data reported on the CRF/eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Investigator Site File.

10.7 Study and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

10.8 Monitoring of the Study

All aspects of the study will be carefully monitored by the Sponsor or designee for compliance with GCP and applicable government regulations.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Investigators and institutions involved in the study will permit study-related monitoring, Sponsor/CRO audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and study records.

The Investigator will promptly notify the Sponsor and the CRO of any inspections scheduled by any regulatory authorities and promptly forward copies of any inspection reports received to the Sponsor.

10.9 Publications

Following completion of the study, the results from the study will be publicly disclosed through posting the results on appropriate registries such as ww.clinicaltrials.gov and may be reported publicly by making any oral public presentation and/or submitting or presenting a manuscript, abstract, or other materials relating to the Study at scientific meetings and/or to a publisher, reviewer, or other outside person in scientific journals (“Publication”), provided; however, that Publication of the results from an individual site shall not be made before the first multi-site Publication by Sponsor. The Sponsor shall coordinate the drafting, editing, authorship, and other activities related to study Publication and shall mutually agree with the Investigator(s) on the number, medium, forum, and timing for Publication. The Sponsor shall solicit input regarding contents of the Publication from all Investigators and in consultation with all sites. The Sponsor acknowledges the right of the Investigator(s) to publish the results of this study after the entire study has completed, but also reserves the right to a window to review the Publication for regulatory compliance as well as for protection of its intellectual property. In particular, the Sponsor may request to remove the Sponsor’s confidential information and suspend Publication for a certain period of time to protect the Sponsor’s intellectual property interest, as further set forth in the Clinical Trial Agreement with the clinical study site(s) and Investigator(s).

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12 Appendices

12.1 Appendix: Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG performance status grades as indicated below:

Grade	Definition
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

12.2 Appendix: Response Assessment of Hodgkin and NonHodgkin Lymphoma (Lugano Classification)

Response/Site	PET-CT-Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response** (all of the following)
Lymph nodes and extralymphatic sites	• Score 1, 2, or 3* with or without a residual mass on 5PS** Note: Uptake may be greater than normal mediastinum and/or liver in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors). In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	• Target nodes/nodal masses must regress to ≤ 1.5 cm in LD • No extralymphatic sites of disease
Nonmeasured lesion	• Not applicable	• Absent
Organ enlargement	• Not applicable	• Regress to normal
New lesions	• None	• None
Bone marrow	• No evidence of FDG-avid disease in marrow	• Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission** (all of the following)
Lymph nodes and extralymphatic sites	• Score 4 or 5** with reduced uptake compared with baseline and residual mass(es) of any size. • At interim, these findings suggest responding disease. • At end of treatment, these findings indicate residual disease.	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm × 5mm as the default value. • When no longer visible, 0 × 0 mm • For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation

Nonmeasured lesion	• Not applicable	• Absent/normal, regressed, but no increase
Organ enlargement	• Not applicable	• Spleen must have regressed by > 50% in length beyond normal
New lesions	• None	• None
Bone marrow	• Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	• Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	• Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	• < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	• Not applicable	• No increase consistent with progression
Organ enlargement	• Not applicable	• No increase consistent with progression
New lesions	• None	• None
Bone marrow	• No change from baseline	• Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease** (requires at least 1 of the following)
Individual target nodes/nodal masses	• Score 4 or 5 with an increase in intensity of uptake from baseline and/or	• PPD progression

Extranodal lesions	• New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	An individual node/lesion must be abnormal with: • LDi > 1.5 cm and • Increase by ≥ 50% from PPD nadir and • An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly
Nonmeasured lesions	• None	• New or clear progression of preexisting nonmeasured lesions
New lesions	• New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	• New or recurrent FDG-avid foci	• New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Nonnodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

** PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Reference: Cheson, 2014

12.3 Appendix: FACT-Lym

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

PHYSICAL WELL-BEING

	Not at all	A little bit	Some what	Quite a bit	Very much
GP1 I have a lack of energy	0	1	2	3	4
GP2 I have nausea	0	1	2	3	4
GP3 Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4 I have pain	0	1	2	3	4
GP5 I am bothered by side effects of treatment	0	1	2	3	4
GP6 I feel ill	0	1	2	3	4
GP7 I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

	Not at all	A little bit	Some what	Quite a bit	Very much
GS1 I feel close to my friends	0	1	2	3	4
GS2 I get emotional support from my family	0	1	2	3	4
GS3 I get support from my friends	0	1	2	3	4
GS4 My family has accepted my illness	0	1	2	3	4
GS5 I am satisfied with family communication about my illness	0	1	2	3	4
GS6 I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1 *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next*					
GS7 I am satisfied with my sex life	0	1	2	3	4

EMOTIONAL WELL-BEING

	Not at all	A little bit	Some what	Quite a bit	Very much
I feel sad	0	1	2	3	4
I am satisfied with how I am coping with my illness	0	1	2	3	4
I am losing hope in the fight against my illness	0	1	2	3	4
I feel nervous	0	1	2	3	4
I worry about dying	0	1	2	3	4
I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL-BEING

	Not at all	A little bit	Some what	Quite a bit	Very much
I am able to work (include work at home)	0	1	2	3	4
My work (include work at home) is fulfilling	0	1	2	3	4
I am able to enjoy life	0	1	2	3	4
I have accepted my illness	0	1	2	3	4
I am sleeping well	0	1	2	3	4
I am enjoying the things I usually do for fun	0	1	2	3	4
I am content with the quality of my life right now	0	1	2	3	4

ADDITIONAL CONCERNS

	Not at all	A little bit	Some what	Quite a bit	Very much
I have certain parts of my body where I experience pain	0	1	2	3	4
I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or	0	1	2	3	4
I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
I have night sweats	0	1	2	3	4
I am bothered by itching	0	1	2	3	4
I have trouble sleeping at night	0	1	2	3	4
I get tired easily	0	1	2	3	4
I am losing weight	0	1	2	3	4
I have a loss of appetite	0	1	2	3	4
I have trouble concentrating	0	1	2	3	4
I worry about getting infections	0	1	2	3	4
I worry that I might get new symptoms of my illness	0	1	2	3	4
I feel isolated from others because of my illness or treatment	0	1	2	3	4
I have emotional ups and downs	0	1	2	3	4
Because of my illness, I have difficulty planning for the future	0	1	2	3	4

12.4 Appendix: Katz Activities of Daily Living

KATZ INDEX OF INDEPENDENCE IN ACTIVITIES OF DAILY LIVING (ADL)			
Activities Points (1 or 0)	Only one option per row		
BATHING - either sponge bath, tub bath, or shower **Points:_____**	**(1 POINT)** Receives no assistance (gets in and out of tub by self if tub is usual means of bathing)	**(1 POINT)** Receives assistance in bathing only one part of the body (such as back or a leg)	**(0 POINTS)** Receives assistance in bathing more than one part of the body (or not bathed)
DRESSING - gets clothes from closets and drawers - including underclothes, outer garments and using fasteners (including braces if worn) **Points:_____**	**(1 POINT)** Gets clothes and gets completely dressed without assistance	**(1 POINT)** Gets clothes and gets dressed without assistance except for assistance in tying shoes	**(0 POINTS)** Receives assistance in getting clothes or in getting dressed, or stays partly or completely undressed
TOILETING - going to the "toilet room" for bowel and urine elimination; cleaning self after elimination, and arranging clothes **Points:_____**	**(1 POINT)** Goes to "toilet room", cleans self, and arranges clothes without assistance (may use object for support such as cane, walker, or wheelchair and may manage night bedpan or commode, emptying same in morning)	**(0 POINTS)** Receives assistance in going to "toilet room" or in cleansing self or in arranging clothes after elimination or in use of night bedpan or commode	**(0 POINTS)** Doesn't go to room termed "toilet" for the elimination process
TRANSFERRING **Points:_____**	**(1 POINT)** Moves in and out of bed as well as in and out of chair without assistance (may be using object for support such as cane or walker)	**(0 POINTS)** Moves in or out of bed or chair with assistance	**(0 POINTS)** Doesn't get out of bed
CONTINENCE **Points:_____**	**(1 POINT)** Controls urination and bowel movement completely by self	**(0 POINTS)** Has occasional “accidents"	**(0 POINTS)** Supervision helps keep urine or bowel control; catheter is used, or is incontinent

KATZ INDEX OF INDEPENDENCE IN ACTIVITIES OF DAILY LIVING (ADL)			
FEEDING **Points:_____**	**(1 POINT)** Feeds self without assistance	**(1 POINT)** Feeds self except for getting assistance in cutting meat or buttering bread	**(0 POINTS)** Receives assistance in feeding or is fed partly or completely by using tubes or intravenous fluids
Total score: _____ SCORING: 6 = High (*patient independent*) 0 = Low (*patient very dependent)*			

Reference: Based on Katz et al, *JAMA, 1963*

12.5 Appendix: Modified Instrumental Activities of Daily Living

MODIFIED INSTRUMENTAL ACTIVITIES OF DAILY LIVING			
Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).			
A. Ability to Use Telephone		**E. Laundry**	
1. Operates telephone on own initiative, looks up	1	1. Does personal laundry completely	1
2. Dials a few well-known numbers	1	2. Launders small items-rinses socks, stockings, etc.	1
3. Answers telephone but does not dial	1	3. All laundry must be done by others	0
4. Does not use telephone at all	0		
5. Not applicable	1	4. Not applicable	1
B. Shopping		**F. Mode of Transportation**	
1. Takes care of all shopping needs independently	1	1. Travels independently on public transportation or drives own car	1
2. Shops independently for small purchases	0	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Needs to be accompanied on any shopping trip	0	3. Travels on public transportation when accompanied by another	1
4. Completely unable to shop	0	4. Travel limited to taxi or automobile with assistance	0
		5. Does not travel at all	0
5. Not applicable	1	6. Not applicable	1
C. Food Preparation		**G. Responsibility for Own Medications**	
1. Plans, prepares and serves adequate meals independently	1	1. Is responsible for taking medication in correct dosages at correct time	1
2. Prepares adequate meals if supplied with ingredients	0	2. Takes responsibility if medication is prepared in advance in separate dosage	0
3. Heats, serves, and prepares meals but does not maintain adequate diet	0	3. Is not capable of dispensing own medication	0
4. Needs to have meals prepared and served	0		
5. Not applicable	1	4. Not applicable	1
D. Housekeeping		**H. Ability to Handle Finances**	
1. Maintains house alone or with occasional assistance (e.g., "heavy work domestic help")	1	1. Manages financial matters independently (budgets, writes cheques, pays rent, bills, goes to bank), collects and keeps track of income	1
2. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1	2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Needs help with all home maintenance tasks	1	3. Incapable of handling money	0
4. Does not participate in any housekeeping tasks	0		
5. Not applicable	1	4. Not applicable	1
Score		**Score**	
		Total score	

Reference: Merli et al. *J Clin Oncol*. 2021 and associated webtool https://redcap.filinf.it/surveys/?s=89AFXML8AK

12.6 Appendix: Modified Cumulative Illness Rating Scale - Geriatric

MODIFIED CUMULATIVE ILLNESS RATING SCALE (CIRS-G)

Each system* is *rated* as *follows:

0 =	**NONE**: No impairment to that organ/system
1 =	**MILD**: Impairment does not interfere with normal activity; treatment may or may not be required; Prognosis is excellent. (Examples could be skin lesions, hernias, or hemorrhoids)
2 =	**MODERATE**: Impairment interferes with normal activity; treatment is needed; prognosis is good. (Examples could be gallstones, diabetes, or fractures)
3 =	**SEVERE**: Impairment is disabling; treatment is urgently needed; prognosis is guarded. (Examples could be resectable carcinoma, pulmonary emphysema, or congestive heart failure)
4 =	**EXTREMELY SEVERE**: Impairment is life threatening; treatment is urgent or of no avail; prognosis is grave. (Examples could be myocardial infarction, cerebrovascular accident, gastrointestinal bleeding, or embolus).

Sr. No.	System	Rating (0-4)
1.	**Cardiac** (heart only)	
2.	**Hypertension** (rating is based on severity; affected systems are rated separately)	
3.	**Vascular** (blood, blood vessels and cells, marrow, spleen, lymphatics)	
4.	**Respiratory** (lungs, bronchi, trachea below the larynx)	
5.	**EENT** (eye, ear, nose, throat, larynx)	
6.	**Upper GI** (esophagus, stomach, duodenum, biliary and pancreatic trees; do not include diabetes)	
7.	**Lower GI** (intestines, hernias)	
8.	**Hepatic** (liver only)	
9.	**Renal** (kidneys only)	
10.	**Other GU** (ureters, bladder, urethra, prostate, genitals)	
11.	**Musculo-Skeletal-Integumentary** (muscles, bone, skin)	
12.	**Neurological** (brain, spinal cord, nerves; do not include dementia)	
13.	**Endocrine-Metabolic** (includes diabetes, diffuse infections, infections, toxicity)	
14.	**Psychiatric/Behavioral** (includes dementia, depression, anxiety, agitation, psychosis)	

How many Ratings of 2 : _____ How many Ratings of 3-4 : _____

Reference: Based on Parmelee et al. *J Am Geriatr Soc* 1995