Combining Loncastuximab Tesirine and Epcoritamab in Relapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL)

Short title: CLEAR

Sponsor: Universität Münster
Schlossplatz 2
48149 Münster

Coordinating investigator:
Univ.-Prof. Dr. med. Georg Lenz
Medizinische Klinik A
Hämatologie, Hämostaseologie, Onkologie und Pneumologie
Universitätsklinikum Münster
Albert-Schweitzer-Campus 1, Gebäude A1
48149 Münster

Biometry:
Dr. rer. med. habil. Marita Ziepert
Institut für Medizinische Informatik, Statistik und Epidemiologie
Universität Leipzig
Härtelstrasse 16-18
04107 Leipzig

Study Contact
E-mail: clear@ukmuenster
Tel. Hotline: + 49 - (0)251 / 83 - 57106 (ZKS Münster) or - 47450 (Studienbüro Med. A)

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1. GENERAL INFORMATION

1.1. Responsible persons, institutions, committees

Sponsor according to German Drug Law (AMG)	Universität Münster Univ.-Prof. Dr. med. Frank Ulrich Müller Albert-Schweitzer-Campus 1, Gebäude D3 48149 Münster Tel: +49 - (0)251 / 83 - 52263 Fax: +49 - (0)251 / 83 - 55004 E-mail: dekanmed@ukmuenster.de
Coordinating investigator	Univ.-Prof. Dr. med. Georg Lenz Universitätsklinikum Münster Medizinische Klinik A Hämatologie, Hämostaseologie, Onkologie und Pneumologie Albert-Schweitzer-Campus 1, Gebäude A1 48149 Münster Tel.: +49 - (0)251 / 83 - 47587 Fax: +49 - (0)251 / 83 - 46019 E-Mail: Georg.Lenz@ukmuenster.de
Central study office	Medizinische Klinik A Hämatologie, Hämostaseologie, Onkologie und Pneumologie Universitätsklinikum Münster Albert-Schweitzer Campus 1, Gebäude A1 48149 Münster Tel.: +49 - (0)251 / 83 - 47450 Fax: +49 - (0)251 / 83 - 46019 E-mail: clear@ukmuenster.de

Biometry and database	Dr. rer. med. habil. Marita Ziepert, Dr. rer. nat. Bettina Altmann Institut für Medizinische Informatik, Statistik und Epidemiologie Universität Leipzig Härtelstraße 16-18 04107 Leipzig Tel.: +49 - (0)341 / 97 - 16120 Fax: +49 - (0)341 / 97 - 16109 E-Mail: marita.ziepert@imise.uni-leipzig.de
SAE Management (Safety Desk)	Dr. med. Trude Butterfaß-Bahloul Zentrum für Klinische Studien Universität Münster Von-Esmarch-Str. 62 48149 Münster Tel.: +49 - (0)251 / 83 - 57109 SAE Fax: +49 - (0)251 / 83 - 57112 E-mail: mssd@ukmuenster.de
Monitoring	Monitoring (Germany): Zentrum für Klinische Studien Universität Münster Von-Esmarch-Str. 62 48149 Münster Monitoring (Italy): Yghea | Ecol Studio S.p.A. Via Rivani 99, 40138 - Bologna (Italy)

Study management	Dr. rer. nat. Tobias Kewitz Zentrum für Klinische Studien Universität Münster Von-Esmarch-Str. 62 48149 Münster Tel.: +49 - (0)251 / 83 - 57106 Fax: +49 - (0)251 / 83 - 57026 E-mail: tobias.kewitz@ukmuenster.de
Data management	Sonja Baier Zentrum für Klinische Studien Universität Münster Von-Esmarch-Str. 62 48149 Münster Tel.: +49 - (0)251 / 83 - 57496 Fax: +49 - (0)251 / 83 - 57026 E-mail: sonja.baier@ukmuenster.de
Reference pathology	Coordinating reference pathologist: Univ.-Prof. Dr. med. Andreas Rosenwald Institut für Pathologie Universität Würzburg Josef-Schneider-Straße 2 97080 Würzburg Tel.: +49 - (0)931 / 201 - 47424 Fax: +49 - (0)931 / 201 - 47440 E-Mail: rosenwald@uni-wuerzburg.de

Pharmacy	Universitätsklinikum Münster Apotheke Abteilung für klinische Studien Albert-Schweitzer-Campus 1 Gebäude A3 48149 Münster Tel.: +49 (0)251 / 83 - 45828 Fax: +49 (0)251 / 83 - 45824 E-mail: apotheke-studien@ukmuenster.de
Protocol Committee	Univ. Prof. Dr. med. G. Lenz, Münster, Germany (chair) Prof. Dr. med. N. Schmitz, Münster, Germany (vice-chair) Prof. Dr. med. B. Glaß, Berlin-Buch, Germany Univ. Prof. Pier Luigi Zinzani, Bologna, Italy
Scientific Advisory Board	The Scientific Advisory Board decides on the conduct and support of scientific projects accompanying this study. Prof. Dr. med. Georg Lenz will act as chairman of the scientific advisory board for this study.
Data Safety Monitoring Committee	Prof. Dr. med. U. Bacher, Bern, Switzerland Prof. Dr. med. M. Herold, Erfurt, Germany Univ. Prof. Dr. rer. biol. hum., Dipl.-Math. Eva Hoster, München, Germany
Financial support	Swedish Orphan Biovitrum AB (Sobi) AbbVie Inc. (AbbVie)
Provider of loncastuximab tesirine and epcoritamab vials	Sobi AbbVie

1.2. Signatures

Sponsor:
Universität Münster
represented by
Univ.-Prof. Dr. med. Frank Ulrich Müller
Dean, Faculty of Medicine

Univ.-Prof. Dr. Frank Ulrich Müller
Dekan
Medizinische Fakultät der Universität Münster
Albert-Schweitzer-Campus 1, Gebäude D3
48149 Münster

15/04/26

Place, date

F. Müller

Signature

Coordinating investigator:
Univ.-Prof. Dr. med. Georg Lenz
Medizinische Klinik A
Hämatologie, Hämostaseologie,
Onkologie und Pneumologie
Universitätsklinikum Münster

Münster, 14.4.26

Place, date

Signature

Biometry:
Dr. rer. med. habil. Marita Ziepert
Institut für Medizinische Informatik,
Statistik und Epidemiologie
Universität Leipzig

Leipzig, 09.04.2026

Place, date

M. Ziepert

Signature

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Investigator:

Place, date

Name

Signature

1.3. Synopsis

	Combining **L**oncastuximab Tesirine and **E**pcorit**a**mab in **R**elapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL)
Short title of study:	CLEAR
Sponsor's Study Code:	WWU23_0006
EU CT Number:	2023-509861-19-00
Sponsor:	Universität Münster
Coordinating investigator:	Univ.-Prof. Dr. med. Georg Lenz Medizinische Klinik A Hämatologie, Hämostaseologie, Onkologie und Pneumologie Universitätsklinikum Münster
Indication:	Second-line therapy for patients 18 years or older with CAR-T cell naive relapsed or refractory aggressive diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBL) or follicular lymphoma (FL) grade 3B or Third-line therapy for patients 18 years or older with relapsed or refractory aggressive DLBCL, HGBCL or FL grade 3B who failed CAR-T cell therapy in second line At least 50% of all study patients will be CAR-T cell naive.
Study design:	Prospective, multicenter, single-arm, open-label, phase II study with a safety run-in (irrespective of CAR-T status) and efficacy run-in (CAR-T naive patients only) phases.
Investigational Medicinal Products:	Loncastuximab tesirine intravenously (iv) Epcoritamab subcutaneously (sc)
Treatment:	Treatment will be initiated with loncastuximab tesirine iv 7 days prior to initiation of epcoritamab. **Loncastuximab tesirine** Loncastuximab tesirine 150 µg/kg iv for 2 cycles followed by 75 µg/kg iv on day 1 of each 21-day cycle in responding patients for 4 cycles subsequently (max. 6 cycles).

	Epcoritamab Step-up dosing for epcoritamab sc will be performed, consisting of a 0.16 mg sc priming dose on day 1 of cycle 1 (day 8 of cycle 1 for loncastuximab tesirine), followed by a 0.8 mg sc dose on day 8, and full dosing with 48 mg sc on day 15. Starting from day 15, epcoritamab will be administered weekly during cycle 2-3, then once every 2 weeks during cycle 4-9, and once every 4 weeks from cycle 10 until cycle 13 (max. 13 cycles).
	For both agents the doses approved according to SmPC are not allowed to be exceeded (i.e. 150 µg for loncastuximab tesirine and 48 mg for epcoritamab).
Primary objective:	Best overall response rate (complete plus partial remission rate) (BORR) in the study population achieved up to 12-months of treatment with loncastuximab tesirine and epcoritamab
Secondary objectives:	**Secondary objectives for efficacy:** - Progression-free survival (PFS) - Overall survival (OS) - Complete remission (CR) rate - Partial remission (PR) rate - Time to complete response - Time to best response - Duration of response (DOR) - Progression rate - Relapse rate - Outcomes according to biological characteristics of the lymphoma **Secondary objectives for safety and tolerability**: - Rate of treatment-related deaths - Safety and tolerability, and protocol adherence of epcoritamab and loncastuximab tesirine
Primary endpoint:	Best overall response rate (BORR) of relapsed/refractory DLBCL, HGBL and FL grade 3B patients defined as the proportion of patients who achieve a complete or partial remission as best response up to 12-months of treatment according to the 2014 Lugano criteria after failing first-line immunochemotherapy administered at least one time or second-line therapy with CAR-T cells.

Secondary endpoints:	**Secondary endpoints for efficacy:** - PFS - OS - CR rate

	- PR rate - Time to complete response - Time to best response - DOR - Progression rate - Relapse rate - Outcomes according to biological characteristics of DLBCL (response rate, PFS, OS, incidence of relapse/refractory disease) **Secondary endpoints for safety and tolerability:** - Adverse events (AEs) - Serious AEs (SAEs) - Rate of treatment related deaths **Secondary endpoints for protocol adherence:** - Number of treatment cycles received - Duration of treatment cycles - Cumulative doses of loncastuximab tesirine and epcoritamab
Study population:	Patients older than 18 years with DLBCL, HGBL or FL grade 3B who failed first-line immunochemotherapy administered at least one time. Patients older than 18 years with DLBCL, HGBL or FL grade 3B who failed second-line therapy with CAR-T cells.
Patient number:	120 patients with histologically confirmed relapsed/refractory DLBCL, HGBL or FL grade 3B, including 20 patients treated in the safety run-in phase (irrespective of CAR-T status) and 20 patients treated in the efficacy run-in phase (CAR-T naive only). The number of patients with previous CAR-T treatment will be capped at n=60.
Number of Study Centers:	A maximum of 38 institutions will be included with sites active in the German Lymphoma Alliance (GLA) (35 institutions) and the Italian Study Group Fondazione Italiana Linfomi (FIL) (3 institutions)

Inclusion Criteria:	**<u>Disease/Condition Activity:</u>** 1. Subjects with histologically confirmed relapsed/refractory (r/r) disease based on pathology report (WHO 2022 criteria) at the time before study entry. Specifically, patients with a. DLBCL (*de novo* or transformed) b. HGBL with *MYC* and *BCL2* rearrangements c. HGBL, not otherwise specified (NOS) d. Follicular lymphoma grade 3B will be included Paraffin-embedded tissue must be available and sent to a reference pathologist in order to allow for pathological diagnosis and the translational research program. CD20 expression (or a high likelihood of CD20 expression) based on immunohistochemistry should be documented prior enrollment into the study. **Refractory disease** is defined as no remission to the last therapy. Subjects intolerant to previous therapy are excluded. Two groups of patients are eligible: - Progressive disease (PD) or stable disease (SD) as best response to previous therapy. - Complete (CR) or partial response (PR) as the best response after previous therapy, with biopsy-proven relapse occurring < 6 months after end of treatment. **Relapsed disease** is defined as subjects achieving complete or partial remission to previous therapy, followed by biopsy-proven relapse ≥6 months after treatment completion. Subjects with refractory and early relapsed (≤12 months) disease after first line anti-CD20-/anthracycline-containing therapy are eligible. Subjects with late relapsed (>12 months) disease after first line anti-CD20-/anthracycline-containing therapy can be enrolled in the study only if deemed ineligible to high dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) or if refuse to undergo HDCT/ASCT. Subjects relapsed/refractory to second line CAR-T cell therapy are eligible. 2. Subjects must be age 18 years or older. 3. Subjects must be eligible to receive and in need of treatment initiation based on symptoms and/or disease burden, as assessed by the investigator.

	4. Eastern Cooperative Oncology Group Performance status (ECOG) 0-2. 5. Subjects must have one or more measurable disease sites, defined as follows: - A positron emission tomography/computed tomography (PET/CT) scan demonstrating PET-positive lesion(s). - At least one measurable nodal lesion (long > 1.5 cm and short axis > 1.0 cm) or one measurable extra-nodal lesion (long axis > 1.0 cm) on CT scan or MRI. 6. Ability to understand and willingness to sign written informed consent. Signed informed consent must be obtained before any study-specific procedure. **Contraception:** 7. Women of childbearing potential and sexually active men must practice a highly effective method of birth control during and after the study, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. 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 giving informed consent until at least 7 months after the patient receives his last dose of study treatment. Men must agree not to donate sperm from the time of giving informed consent until at least 7 months after the patient receives his last dose of study treatment. For female subjects, they apply for 12 months after the last dose of the study drug. 8. Women of childbearing potential must have a negative serum or urine beta-human chorionic gonadotropin (beta-hCG) pregnancy test at screening. **Adequate baseline organ function tests should be collected no more than 7 days before starting study treatment. The following criteria should be met:** 9. Total bilirubin ≤ 1.5 times the upper limit of normal (ULN) (< 3 times ULN for patients with Gilbert syndrome, cholestasis due to compressive adenopathies of the hepatic hilum, documented liver involvement, or biliary obstruction due to lymphoma). 10. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and gamma glutamyl

	transferase (GGT) ≤ 2.5 times ULN (≤ 5 times ULN for patients with liver involvement by lymphoma). 11. Glomerular filtration rate (GFR) ≥ 45 mL/min/1.73 m² according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. If not within the target range, this evaluation may be repeated once after at least 24 hours, either using the CKD-EPI formula or through 24-hour sampling. If the subsequent result falls within an acceptable range, it may be used to fulfill the inclusion criteria. 12. Prothrombin time/International normalized ratio (INR)/Activated partial thromboplastin time (aPTT) ≤ 1.5 times ULN, unless the patient is receiving anticoagulation (although INR should not exceed 4.0). 13. Platelet count ≥ 75,000/mm³ without transfusion in the prior 7 days. 14. Hemoglobin ≥ 8 g/dL. 15. Absolute neutrophil count ≥ 1,000/mm³ (off growth factors at least 72 hours). 16. Left ventricular ejection fraction > 45%. **Concomitant Medications:** 17. Subjects should not take medication known to decrease T-cell numbers or activity, or other concurrent immunosuppressive medication, except for up to 10 mg prednisone daily or its equivalent, unless it is for disease control during screening,

	premedication and/or CRS/ICANS management within the study. 18. Subjects must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drugs, nor be currently enrolled in another interventional clinical study or have been previously enrolled in this study (agents that have been approved under emergency authorization, e.g., anti-SARS-CoV-2 monoclonal antibodies, are allowed). 19. Acute toxicity (except alopecia, fatigue) of any prior lymphoma therapy should be resolved to Grade ≤ 1 (with the exception of prior CRS or ICANS that should be fully resolved) at study screening. 20. Subjects should not have received vaccination with live-attenuated vaccines within 28 days prior to screening, nor are expected to need any live-attenuated vaccination during study participation, including at least 3 months following the last dose of study treatment. However, coronavirus mRNA and adenovirus-based vaccines, which are not live-attenuated vaccines, are permitted.

Exclusion Criteria:	**Patients who meet any of the following criteria at the time of screening will be excluded:** 1. Any prior lymphoma-directed treatment, except for first-line anti-CD20-/anthracycline-containing therapy or second line CAR-T cell therapy. Particularly, patients previously treated with loncastuximab tesirine and any CD3xCD20 bispecific antibody therapy are not eligible. 2. Patients with late relapse (>12 months) after first-line immunochemotherapy considered HDCT/ASCT eligible as assessed by the local investigator. 3. Known central nervous system (CNS) involvement. 4. Diagnosed or treated for any malignancy other than DLBCL, transformed indolent lymphoma, HGBL or FL grade 3B within the last 3 years, except for the following: - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. - Non-invasive basal cell or squamous cell skin carcinoma. - Adequately treated carcinoma *in situ* without evidence of disease. - Localized prostate cancer, post-radical prostatectomy with non-rising prostate-specific antigen levels < 0.1 ng/mL. - Cervical carcinoma of stage 1B or less. - Non-invasive, superficial bladder cancer. - Any curable cancer with a CR of > 2 years duration. 5. Known history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or active hepatitis B virus (HBV) infection or any known active systemic bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds). Patients with serologic markers of HBV immunization due to vaccination (HBsAg negative, Anti-HBc negative, and Anti-HBs positive) will be eligible. Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. 6. CMV-PCR positive at baseline. 7. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or interfere with the feasibility to administer study drugs, including active hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS), history

	of cutaneous collagenous vasculopathy and capillary leak syndrome. 8. Concurrent treatment with another investigational agent or radiation therapy. 9. Any psychological, cognitive, familial, or social condition that, in the investigator's opinion, compromises the patient's ability to understand the patient information, give informed consent, or comply with the study protocol. 10. Participation in another clinical trial. 11. Known history of hypersensitivity and/or positive serum human anti-drug antibody (ADA) against any component of the study products or concomitant medication or an anti-CD19 antibody. 12. History of Stevens-Johnson syndrome or toxic epidermal necrolysis. 13. 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; history of pericardial effusion to exclusion criteria). 14. Pregnancy or breastfeeding. 15. Use of any other experimental medication within 30 days or 5 half-lives prior to the start of study drug (Cycle 1 Day 1). 16. Close affiliation with the investigational site, such as a close relative of the investigator or dependent persons (e.g., employee or student of the investigational site). **<u>Excluded medical conditions:</u>** 17. Congestive heart failure > New York Heart Association (NYHA) class 2. 18. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). 19. Uncontrolled atrial or ventricular cardiac arrhythmia. 20. Left ventricular ejection fraction ≤ 45%. 21. Electrocardiographic evidence of acute ischemia, coronary angioplasty, or myocardial infarction within 6 months prior to screening. 22. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within 3 months before the start of study medication. 23. Congenital long QT syndrome or a QTcF interval of > 480 ms at screening (unless secondary to pacemaker or bundle branch block). 24. Severe chronic pulmonary disease.

	25. Known clinically significant liver disease, including hepatitis, current alcohol abuse, or cirrhosis. 26. Autoimmune disease requiring immunosuppressive therapy except for up to 10 mg prednisone daily (or equivalent). 27. Seizure disorder requiring therapy within the past 12 months. Subjects with history of seizure disorder beyond that must have complete CNS workup. 28. Major surgery within 4 weeks of the first dose of study drugs excepting lymphoma-related reasons. 29. Any other co-existing medical or psychological condition that will preclude participation in the study or compromise ability to give informed consent.

Visits:	**Screening visit:** Patients will undergo a screening visit prior to any treatment to verify study eligibility. **Treatment period:** Patients will receive loncastuximab tesirine for up to 6 cycles if no disease progression or relapse, unacceptable safety and tolerability, death, major protocol deviation, or patient, investigator, or sponsor decision. Epcoritamab will be administered for up to one year (max. 13 cycles) if no disease progression or relapse, unacceptable safety and tolerability, death, major protocol deviation, or patient, investigator, or sponsor decision . **Restaging:** There will be repeated staging (response assessment) every 6 weeks for first 6 months after starting treatment, then every 3 months for subsequent 6 months, and every 6 months thereafter and as clinically indicated until the end of treatment. Staging should be preferably PET-based; contrast-enhanced CT is also accepted if PET-CT or PET-MRI is not available. **Follow-up visits:** For all study patients, a first follow-up should be performed 6 weeks after the end of therapy with loncastuximab tesirine and epcoritamab. Three-monthly follow-up examinations are recommended during the first 2 years after the end of therapy, and six-monthly evaluation in the following 3 years. Safety evaluations include adverse event (AE) monitoring, physical examination, evaluation of changes to concomitant medications, and clinical laboratory parameters (hematology, coagulation, and serum chemistry). AEs that occur between the signing of the informed consent through 150 days after the last application of loncastuximab tesirine and/or epcoritamab will be collected. The severity of adverse events will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0. Serious adverse events will be reported according to the Good Clinical Practice (GCP) regulations.

Analysis of feasibility and safety:	**Safety run-in phase for all patients:** A first safety analysis will be conducted 60 days after 20 patients started treatment with loncastuximab tesirine and epcoritamab. A detailed analysis of all (serious) adverse events, particularly the occurrence of cytokine release syndrome (CRS), macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), immune effector cell-associated neurotoxicity syndrome (ICANS), tumor lysis syndrome (TLS), as well as liver- and phototoxicity, edema, effusion and infections, will be performed. The toxicities observed will be compared to the (S)AEs experienced in the loncastuximab tesirine phase 2 trial (Caimi et al. Lancet Oncol 2021; 22:790) and the epcoritamab phase 1/2 study (Hutchings et al. Lancet 2021; 398:1157). These data will be submitted to the Clinical Trial Information System (CTIS) as part of a substantial modification for review and decision-making on the continuation of the study. The Data Safety Monitoring Committee (DSMC) will evaluate the safety profile of the combination of epcoritamab and loncastuximab tesirine and decide on the continuation of the study. **Efficacy run-in phase for CAR-T naive patients:** For patients not pretreated with CAR-T cells, an additional and separate efficacy analysis will be performed after the 20th CAR-T naive patient started treatment with loncastuximab tesirine and epcoritamab and had a second response assessment (12 weeks after treatment initiation) by FDG-PET/CT (-/MRI). The primary endpoint of the CLEAR study is BORR. Studies with CAR-T cells performed in second line patients with early relapse/refractory disease, the ZUMA-7 (n=180) and TRANSFORM (n=92) trials, demonstrated an ORR of 83% and 87% respectively. Thus, the pooled ORR of a CAR-T cell therapy is estimated at 84% (95% CI: 79-88%). For the efficacy run-in phase of the CLEAR study a BORR < 60% is considered not acceptable. If ≤ 11/20 patients achieve a CR or PR the BORR will be ≤ 55% (95% CI: 32-77%), no longer including the lower limit of the 95% CI for BORR observed in ZUMA-7 and TRANSFORM trial (pooled data) and the study will be closed for CAR-T naive patients. In any case, the BORR will be reported to the DSMC, the members of which will meet to evaluate the efficacy of CLEAR study in the first 20 CAR-T naive patients included. The DSMC shall recommend continuation of the study, require modifications, or stop the study after independent review of all available data. The results of the efficacy run-in phase evaluated by the DSMC will be communicated and discussed with the principal investigator, the study committee, and the sponsor of the study. The final recommendation to continue, modify or stop the study lies with the DSMC. These data will be submitted to CTIS as well as part of a substantial modification for review and decision-making on the continuation of the study. The

	study sponsor will follow the DSMC's suggestion to continue, modify or stop the study for CAR-naive patients. **<u>Interim safety and efficacy analysis in all patients:</u>** An interim analysis will be conducted 6 months after the 50th patient has been recruited. Patients participating in the safety run-in phase will be considered for interim analysis as well. If the ORR is 60% or below, the study will be terminated early. The relevant data will be submitted to the CTIS as part of a substantial modification for review and decision-making on the continuation of the study. At interim analysis, the members of the DSMC will evaluate the efficacy and safety profile of the combination of epcoritamab and loncastuximab tesirine and the protocol adherence and decide on the continuation of the study.
Statistical Methods:	The ORR, CR rate, PR rate, progression rate, rate of treatment-related deaths and relapse rate will be documented together with the corresponding 95% confidence intervals (Clopper-Pearson). Data on time to event endpoints (PFS, OS, duration of complete response, duration of response) will be analyzed using Kaplan-Meier curves/cumulative incidence curves. Median time for these endpoints will be presented with 95% confidence intervals. For qualitative endpoints (adverse events, serious adverse events) frequency tables will be prepared. Quantitative endpoints (laboratory parameters, cumulative doses of drugs, duration of therapy, time to complete response, time to best response) will be described in tables displaying sample size, range, mean and standard deviation or medians and quartiles.
Analysis population	All analyses will use the intent-to-treat population, which will include all patients who receive any treatment.
Timelines:	First patient in: Q4/2025 Last patient in: Q2/2027 Planned overall duration of the study: 4.5 years
Financial support:	AbbVie Sobi

1.4. Abbreviations

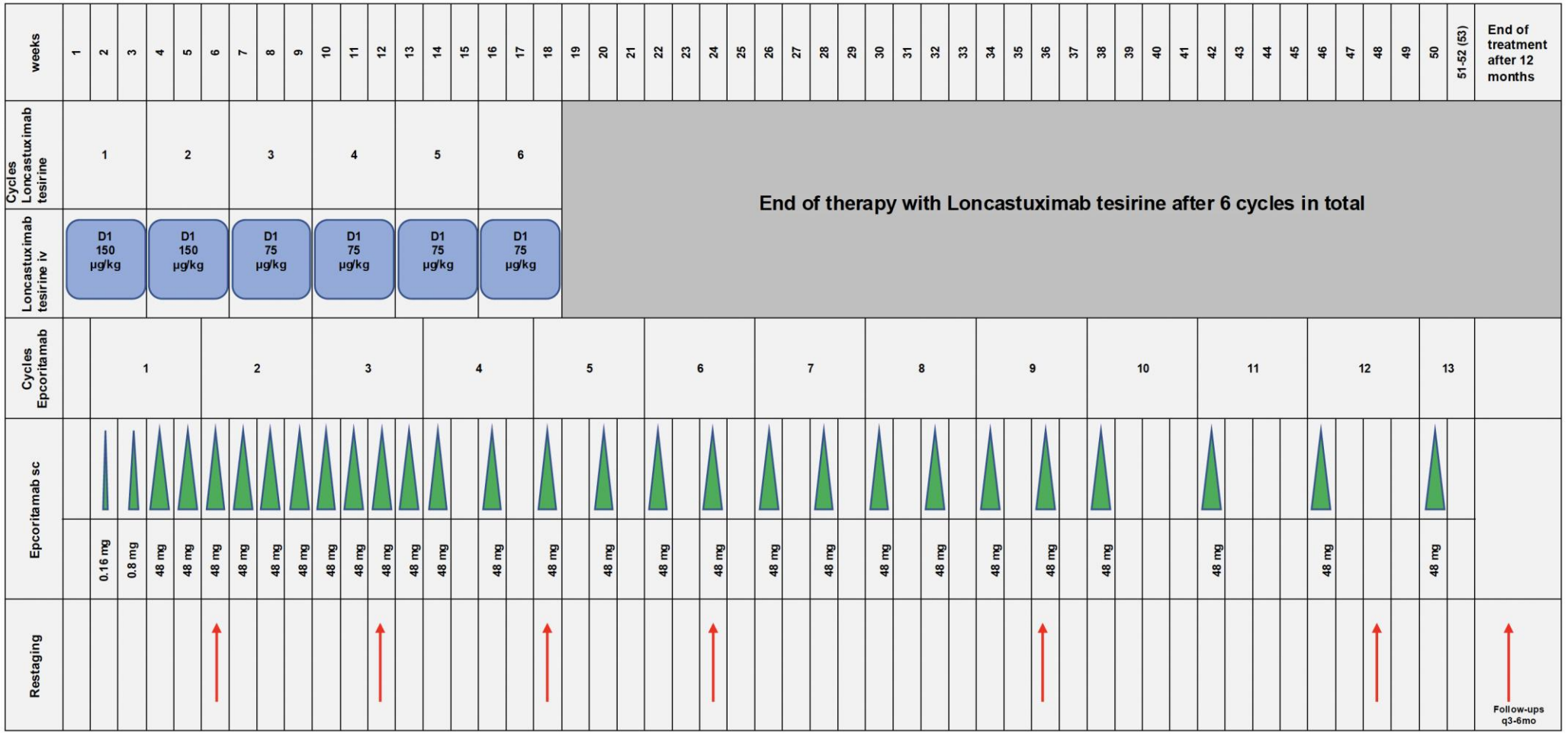
beta-hCG	beta-human chorionic gonadotropin
%CV%	coefficient of variation
ABC	activated B-cell
ABW	adjusted body weight
ADA	anti-drug antibodies
ADC	antibody-drug conjugates
AE	adverse event
AESI	adverse event of special interest
ALT	alanine-aminotransferase
AMG	Arzneimittelgesetz (german drug law)
ANC	absolute neutrophil count
Anti-HBc	hepatitis B core antigen antibodies
Anti-HBs	hepatitis B surface antigen antibodies
ASCT	autologous stem cell transplantation
ASR	annual safety report
AST	aspartate-aminotransferase
ASTCT	Adults American Society for Transplantation and Cellular Therapy
AUC	area under the curve
BCL2	B-cell lymphoma 2
BORR	best overall response rate
BP	blood pressure
BSA	body surface area
BsAbs	bispecific antibodies
BTKi	Bruton's tyrosine kinase inhibitor
C	cycle
CAR	chimeric antigen receptor
CD	cluster of differentiation
cfDNA	cell-free DNA
CHMP	Committee for Medicinal Products for Human Use
CHOP	cyclophosphamide, hydroxyl daunomycin (doxorubicin), oxovincaleukoblastin (vincristine), prednisone
CI	confidence interval
CKD-EPI	chronic kidney disease epidemiology collaboration creatinine equation
CMV	cytomegalovirus
CMR	complete metabolic remission
CTIS	clinical trial information system
PMR	partial metabolic remission
CNS	central nervous system
CR	complete remission
CRF/eCRF	case report form/electronic case report form
CRS	cytokine release syndrome
CRu	complete remission unconfirmed
CSF	csf-spinal fluid
CSP	concomitant scientific program
CT	computer tomography
CTC	common toxicity criteria

CTCAE	common terminology criteria for adverse events
CTIS	Clinical trial information System
CTLC	clinical tumor lysis syndrome
ctDNA	circulating tumor DNA
CTX	chemotherapy
CYP3A	cytochrome P450, family 3, subfamily A
D	day
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DOR	duration of response
DSHNHL	German Non-Hodgkin's Lymphoma Study Group
DSMC	Data Safety Monitoring Committee
DSUR	development safety update report
e.g.	exempli gratia (for example)
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediamine tetra acetic acid
EF	ejection fraction
EFS	event-free survival
EMA	European Medicine Agency
EOT	end of treatment
EudraCT	European Database for Clinical Trials
EV	extracellular vesicle
EV-RNA	extracellular vesicle ribonucleic acid
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	18F-fluorodeoxyglucose positron emission tomography
FeV1	forced expiratory volume in 1 second
FFPE	formalin fixed paraffin embedded
FIL	Fondazione Italiana Linfomi (italian lymphoma foundation)
FISH	fluorescence in-situ hybridization
FL	follicular lymphoma
FSH	follicle-stimulating hormone
GCB	germinal-center B-cell type
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate
GGT	gamma glutamyltransferase
GLA	German Lymphoma Alliance
GLP	good laboratory practice
GnRH	gonadotropin-releasing-hormone
HB	hemoglobin
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDCT	high-dose chemotherapy
HGBL	high grade B-cell lymphoma
HIV	human immunodeficiency virus

HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
i.e.	id est (that is)
iv	intravenous
IB	Investigator's Brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICH	international conference on harmonisation
IF	immunofluorescence
IGRA	interferon gamma release assay
IgRT	immunoglobulin replacement therapy
IHC	immunhistochemistry
IMISE	Institute for Medical Informatics, Statistics and Epidemiology
IMP	investigational medicinal product
INR	international normalized ratio
IPI	international prognostic index
ISF	investigator site file
ITT	intention-to-treat
LDH	lactatdehydrogenase
LFT	liver function test
lonca	loncastuximab tesirine
MAS	macrophage activation syndrome
mAbs	monoclonal antibodies
MedDRA	Medicinal Dictionary for Regulatory Activities
miRNA	microRNA
MRD	measurable residual disease
MRI	magnetic resonance tomography
MTD	maximum tolerated dose
MYC	myelocytomatosis gene
NCI	national cancer institute (US national institute of health)
NGS	next generation sequencing
NHL	non-Hodgkin lymphoma
NIMP	non-investigational medicinal product
NIP	non-infectious pneumonitis
NK	natural killer
NOS	not otherwise specified
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PO	per os, orally
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	disease progression/progressive disease
PET	positron emission tomography
PFS	progression-free survival
PG	pharmacogenomic
PG DNA	pharmacogenomic deoxyribonucleic acid
PI3K	phosphatidylinositol-3-kinase

PJP	pneumocystis jiroveci pneumonia
PK	pharmacokinetic
PMBCL	primary mediastinal large B-cell lymphoma
PP	per-protocol
PR	partial responses
PT	prothrombin time
PTT/aPTT	partial thromboplastin time/activated partial thromboplastin time
QTcF	Fridericia´s QT interval correction formula
Q3MO	once every 3 months
QW	once weekly
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Q4W	once every 4 weeks
R	rituximab
r/r	relapsed/refractory
R-DHAP	rituximab, dexamethasone, high-dose cytarabine, and cisplatin
R-DHAX	rituximab, dexamethasone, high-dose cytarabine, and oxaliplatin
R-DHAC	rituximab, dexamethasone, high-dose cytarabine, and carboplatin
R-GDP	rituximab, gemcitabine, dexamethasone, and cisplatin
R-ICE	rituximab, ifosfamid, carboplatin, and etoposide
RNA	ribonucleic acid
RWS	real-world study
sc	subcutaneously
SAE	serious adverse event
SAP	statistical analyses plan
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus type 2
SAS	safety analysis set
SOC	standard of care
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse (drug) reaction
TB	tuberculosis
TBNK	T-cells, B-cells, and natural killer cells
TEAE	treatment emergent adverse event
TLS	tumor lysis syndrome
TMF	trial master file
TMLV	total metabolic lymphoma volume
TSH	thyroid stimulating hormone
ULN	upper limit of normal value
vs.	versus
WHO	World Health Organisation
WM	Waldenström’s macroglobulinaemia
YR	year
ZKS	Zentrum für klinische Studien (center for clinical studies)
GEMOX	gemcitabine and oxaliplatin
TEAE	treatment emergent adverse event

1.5. Study flow chart



1.6. Tables of activities

Schedule of activities	Screening prior to any therapy (Day -28 to Day -1)	**Loncastuximab tesirine**						
		Cycle 1-5 Day 1 q3w		Cycle 6 Day 1 q3w		EOT loncastuximab tesirine	End of treatment visit	Post-treatment follow-up[16]
Loncastuximab tesirine iv[1]		x		x				
		Epcoritamab						
		Cycle 1-3 Day 1,8,15,22 qw		Cycle 4-9 Day 1,15 q2w		Cycle 10-13 Day 1 q4w	End of treatment Visit	Post-treatment follow-up[16]
Epcoritamab sc[2]		**Each cycle q4w; 0.16 mg D1, 0.8 mg D8, 48 mg from D15 cycle 1; weekly in cycles 1-3; subsequently 1 x q2w cycle 4-9 and 1 x q4w from cycle 10 to cycle 13**						
Laboratory analysis	**Please refer to tables below for details of laboratory analysis**							
Informed consent	x							
Eligibility criteria	x							
Patient's history[3]	x	x	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x	x
Clinical examination[4]	x	x	x	x	x	x	x	x
Height (screening only) and weight[5]	x	x	x	x	x	x		
Performance status (ECOG)	x	x	x	x	x	x	x	x
Echocardiogram	x							
12 lead-electrocardiogram[5]	x	x	x	x	x	x	x	
FDG-PET-CT/ FDG-PET-MRI[6]	x							
MRI scan (brain), lumbar punction[7]	x							
Histology[8]	x							

Schedule of activities	Screening prior to any therapy (Day -28 to Day -1)	**Loncastuximab tesirine**						
		Cycle 1-5 Day 1 q3w		Cycle 6 Day 1 q3w		EOT loncastuximab tesirine	End of treatment visit	Post-treatment follow-up[16]
Loncastuximab tesirine iv[1]		x		x				
		Epcoritamab						
		Cycle 1-3 Day 1,8,15,22 qw		Cycle 4-9 Day 1,15 q2w		Cycle 10-13 Day 1 q4w	End of treatment Visit	Post-treatment follow-up[16]
Epcoritamab sc[2]		**Each cycle q4w; 0.16 mg D1, 0.8 mg D8, 48 mg from D15 cycle 1; weekly in cycles 1-3; subsequently 1 x q2w cycle 4-9 and 1 x q4w from cycle 10 to cycle 13**						
Bone marrow examination[9]	x						x[10]	
Radiographic disease response assessment[10]			c2, c4 lonca		c6 lonca; c6 and c9 epco	c13 epco	x	x
SARS-CoV-2 Test[11]	x							
Hospitalization for CRS monitoring[12]		x						
ICANS assessment/ICE Score[13]	x	x	x	x	x	x	x	
CRS prophylaxis and temperature monitoring[14]		x	x	x	x	x		
AEs and SAEs[15]		x						

1. Loncastuximab tesirine (lonca) 150 µg/kg iv for 2 cycles, followed by 75 µg/kg iv on Day 1 of each 21-day cycle in responding patients, for a maximum of 6 cycles. For reducing a lymphoma burden and decresing the risk of TLS, treatment will be initiated with loncastuximab tesirine iv 7 days prior to the initiation of epcoritamab.
2. Step-up dosing for epcoritamab sc will be performed during cycle 1, consisting of 0.16 mg sc priming dose on Day 1, followed by 0.8 mg sc on Day 8, and subsequent full dosing with 48 mg sc on Day 15 and Day 22. In cycles 2-3, epcoritamab will be administered once every week (QW), followed by once every 2 weeks (Q2W) in cycles 4 to 9. In the consolidation Phase (cycle 10 to cycle 13) epcoritamab will be administered once every 4 weeks (Q4W) or until disease progression or relapse, unacceptable toxicity, death, major protocol deviation, pregnancy, or patient or investigator decision whichever occurs first.
3. This includes constitutional symptoms (B-symptoms): assessment for the presence of drenching night sweats, unintentional weight loss of > 10% of body mass in the previous 6 months, and/or fever > 38°C without identifiable cause.
4. This includes vital signs (blood pressure, heart rate, temperature) prior to and 1 hour (+30 minutes) after epcoritamab administration, as well as prior to the administration of loncastuximab tesirine.
5. Prior to each cycle of loncastuximab tesirine; prior to each cycle (D1) of epcoritamab if clinically indicated.
6. FDG-PET: The procedure is compulsory within 4 weeks (day -28 to -1) before starting treatment and is recommended to be performed as FDG-PET/[full-dose] CT procedure with FDG-PET and diagnostic CT acquisition as a single procedure. Alternatively, FDG-PET/MRI is allowed.
7. Only for patients with clinical suspicion of CNS involvement: MRI scan of the brain, lumbar puncture with CSF cytology, and flow cytometry within 4 weeks (days -28 to -1) before starting treatment.
8. Histological confirmation of the diagnosis of relapsed/refractory aggressive B-cell lymphoma (DLBCL or HGBL) based on an excisional biopsy of a lymph node, an appropriate sample of a lymph node, or extranodal involvement (see Section 11.1) not older than 3 months.
9. Bone marrow cytology, flow cytometry, and histology should be performed as part of staging, not older than 8 weeks prior to enrollment (no indication if FDG-PET at screening is non-suspicious for bone marrow involvement). Bone marrow diagnostics at the end of treatment should be performed only when the bone marrow was initially involved.
10. FDG-PET is highly recommended for radiologic assessment of treatment. If PET-CT or PET-MRI cannot be performed, contrast-enhanced CT scans of the neck, thorax, and abdomen are to be performed. Response assessment according to Lugano criteria. Repeated staging (see Appendix C) every 6 weeks for 6 months after starting treatment, then every 3 months for subsequent 6 months, and every 6 months thereafter until the end of treatment or and as clinically indicated. Example: at the end of cycles 2, 4, 6 of loncastuximab tesirine (lonca) and at the end of cycles 6, 9 and 13 of epcoritamab (epco) within the first year of therapy and 6 months thereafter. In cases of early discontinuation of therapy (see Section 11.6), a restaging examination should be conducted as soon as possible to determine the success of treatment at the time of discontinuation.
11. SARS-CoV-2 rapid antigen test for SARS-CoV-2 infection (only if a subject has signs/symptoms suggestive of SARS-CoV-2 to rule out infection).
12. Hospitalization at C1D15 of epcoritamab or at re-priming (first full dose 48 mg) for CRS monitoring is compulsory.
13. Prior to the administration of epcoritamab. For details, see Appendix E.
14. CRS prophylaxis and temperature monitoring prior to each application of epcoritamab, especially on D1, D8, D15, and D22. CRS prophylaxis consists of Dexamethasone 15 mg daily for cycle 1 or re-priming cycle (Days 1 to 4, 8 to 11, 15 to 18, 22 to 25). The subject should perform self-administered oral temperature monitoring 3 times a day (approximately every 6-8 hours during waking hours) for the first 4 days post-epcoritamab administration. Details in Section 8.4 and Section 9.4.2.
15. The documentation starts with registration within the trial and ends 150 days after the last application of loncastuximab tesirine or epcoritamab (whichever is applied last).
16. A first follow-up should be performed 6 weeks after the end of therapy with study drugs. Thereafter, 3-monthly follow-up examinations are recommended during the first 2 years after the completion of therapy, followed by 6-monthly follow-up visits. Follow-up observation within the study will end for all patients 3 years after the last patient was enrolled in the study. For radiologic assessment during follow-up, CT scan of the neck/thorax/abdomen is accepted (MRI also accepted, neck: ultrasound also accepted). All CT scans performed during the follow-up period later than 6 months after the last restaging are optional. Thus, CT scans should be performed at the first and second follow-up examination.

Tables of activities (laboratory analysis)

Schedule of activities	Screening (Day -28 to Day -1)	Loncastuximab tesirine												
		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5
		D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1
		Epcoritamab												
			Cycle 1				Cycle 2				Cycle 3			
			D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22
Hematology[a]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biochemistry[b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
T3, T4, TSH[c]	x	x			x			x			x			x
Coagulation panel: PT/INR, PTT[d]	x	x			x			x			x			x
Beta2-microglobulin	x													
Lipid panel	x													
Immunglobulins (IgA,IgG, IgM)[e]	x										x			
Cytomegalovirus (CMV) screening[e]	x										x			
HBsAg, HBcAb, anti-HCV, HIV[f]	x													
Tuberculosis screening[g]	x													
Urine analysis[h]	x	x			x			x			x			x
Pregnancy test[i]	x	x			x			x			x			x
TLS (Tumor Lysis Syndrome) chemistry panel[j]			x											
Whole blood ctDNA (MRD)[k]		x					x				x			
Immuno-phenotyping (exploratory)[k]		x	x				x						x	
T-Cells, B-Cells, NK cells (TBNK) by flow cytometry[k]		x	x				x				x			

Tables of activities (laboratory analysis)

Schedule of activities	Loncastuximab tesirine					EOT loncastuximab tesirine																		
	Cycle 5		Cycle 6																					
	D8	D15	D1	D8	D15																			
	Epcoritamab																							
	Cycle 4				Cycle 5				Cycle 6				Cycle 7				Cycle 8				Cycle 9			
	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22
Hematology[a]	x		x		x		x		x		x		x		x		x		x		x		x	
Biochemistry[b]	x		x		x		x		x		x		x		x		x		x		x		x	
T3, T4, TSH[c]			x						x												x			
Coagulation panel: PT/INR, PTT[d]			x						x												x			
Beta2-microglobulin																								
Immunglobulins (IgA,IgG, IgM)[e]									x												x			
Cytomegalovirus (CMV) screening[e]									x												x			
HBsAg, HBcAb, anti-HCV, HIV[f]																								
Tuberculosis screening[g]																								
Urine analysis[h]			x						x				x				x				x			
Pregnancy test[i]			x						x				x				x				x			
Whole blood ctDNA (MRD)[k]									x															
Immuno-phenotyping (exploratory)[k]					x																			
T-Cells, B-Cells, NK cells (TBNK) by flow cytometry[k]									x												x			

Tables of activities (laboratory analysis)

Schedule of activities	EOT Ioncastuximab tesirine														End of treatment visit	Post-treatment follow-up
	Epcoritamab															
	Cycle 10				Cycle 11				Cycle 12				Cycle 13			
	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8		
Hematology[a]	x				x				x				x		x	x
Biochemistry[b]	x				x				x				x		x	x
T3, T4, TSH[c]									x						x	x
Coagulation panel: PT/INR, PTT[d]									x						x	x
Immunglobulins (IgA,IgG, IgM)[e]									x						x	
Cytomegalovirus (CMV) screening[e]									x						x	
HBsAg, HBcAb, anti-HCV, HIV[f]																
Tuberculosis screening[g]																
Urine analysis[h]	x				x				x				x		x	
Pregnancy test[i]	x				x				x				x		x	
ctDNA (MRD)[k]													x		x	
Immuno-phenotyping (exploratory)[k]															x	
T-Cells, B-Cells, NK cells (TBNK) by flow cytometry[k]													x		x	

[a] Blood count with differential blood cell count should be monitored prior to each cycle of loncastuximab tesirine and prior to each application of epcoritamab. During therapy with loncastuximab tesirine, blood count should be monitored twice a week. The scheduling of the second weekly control can be determined by the investigator.

[b] Chemistry panel including sodium, potassium, LDH, calcium, magnesium, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase, creatinine, calculation of GFR by CKD-EPI, BUN, glucose, total protein, albumin, and lipase.

[c] Free T3 and free T4 should be measured if the TSH result is abnormal. Screening should be conducted on Day 1 of each cycle of loncastuximab tesirine.

[d] Screening should be conducted on Day 1 of each cycle with loncastuximab tesirine.

[e] Quantitative monitoring of IgM, IgA, and IgG levels, as well as CMV including CMV-PCR, CMV IgM, and IgG, should be performed at screening. Subsequently, quantitative monitoring of IgM, IgA, IgG, and CMV-PCR should be conducted on Day 1 of each third cycle of epcoritamab (C3, C6, C9, C12) and at the end of treatment.

[f] Patients with positive tests for HBsAg and/or HBcAb will be eligible if they are negative for HBV-DNA. These patients should receive prophylactic antiviral therapy and should undergo HBV-DNA testing with PCR monthly throughout the treatment and for 12 months thereafter. If the viral load becomes positive, the patient should be withdrawn from the study. Patients with a positive test for anti-HCV antibody will be eligible if they are negative for HCV-RNA. These patients should undergo HCV-RNA testing by PCR monthly throughout the treatment and for 12 months thereafter. If the viral load becomes positive, the patient should be withdrawn from the study.

[g] Tuberculosis (TB) screening should be conducted using an interferon gamma release assay (IGRA) if clinically indicated. Clinical indications may include signs and symptoms of TB, contact history, or if the subject lives in or has traveled to or lived in countries with a high TB burden according to the World Health Organization (WHO).

[h] Dipstick including protein, specific gravity, glucose, and blood; performed at baseline and then D1 of every other cycle of loncastuximab tesirine.

[i] Screening: Urine or serum testing is required for females of childbearing potential. Postmenopausal women must have been amenorrheic for ≥ 12 months to be considered "of non-childbearing potential". After cycle 1, a urine or serum pregnancy test (if applicable) should be conducted on Day 1 of every cycle of loncastuximab tesirine and on Day 1 of every cycle of epcoritamab after EOT with loncastuximab tesirine as well as at the end of treatment visit.

[j] Clinical tumor lysis syndrome (CTLS) should be monitored on Day 1 of epcoritamab treatment and subsequently as clinically indicated in subjects while receiving study drug therapy. Please refer to Appendix G for the CTLS chemistry panel.

[k] Please refer to Section 11.2 for details on biomarker sample collection and Appendix H for further information.

2. MEDICAL BACKGROUND AND RATIONALE

2.1. Current results of standard treatment in diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) represents the most common lymphoma entity accounting for roughly 40% of all cases[1]. Overall, while about two-thirds of DLBCL patients can be cured by first-line therapy, one-third of the patients will be primary refractory or will relapse (r/r DLBCL) after an initial response[2, 3]. These patients are characterized by poor outcome with the majority of patients succumbing to their disease[2].

Until recently, the clinical management of r/r DLBCL patients largely depended on their eligibility for high-dose therapy (HDCT) and autologous stem cell transplantation (ASCT). Patients responding (CR, PR) to a platinum-based salvage chemoimmunotherapy with rituximab, gemcitabine, dexamethasone, cisplatin (R-GDP), rituximab, ifosfamide, carboplatin, and etoposide (R-ICE), or rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) were to receive HDCT/ASCT while non-eligible were observed after a combination of rituximab and salvage chemotherapy alone[4, 5]. Patients not responding or relapsing after HDCT/ASCT could be offered chimeric antigen receptor (CAR)-T cell therapy[6, 7]. After publication of two randomized prospective studies comparing salvage chemotherapy followed by HDCT/ASCT with CAR-T cell therapy[8, 9], patients with primary refractory disease or early relapse (<12 months) considered CAR-T cell eligible preferentially receive one of the CAR-T cell products licensed for this indication: Axi-cel (Axicabtagene ciloleucel) or Liso-cel (Lisocabtagene maraleucel). The overall response rate (ORR) of salvage chemotherapy followed by HDCT/ASCT is in the range of 45-50%[3, 4]. In the randomized studies comparing HDCT/ASCT with CAR-T cell therapy ORR rates were 50% vs. 83% and 49% vs. 87%, respectively[8, 9].

Patients with primary refractory disease, not achieving a remission after salvage therapy or relapsing after preceding HDCT/ASCT or CAR-T cell therapy have a dismal prognosis with conventional therapies[2, 4, 10, 11].

2.1.1. New drugs

Treatment results with several new drugs active in r/r DLBCL have recently been reported[3]. Among others, ibrutinib, lenalidomide, polatuzumab vedotin, and tafasitamab have been investigated in phase II and/or phase III studies. Both Bruton's tyrosine kinase (BTK)-inhibitors and lenalidomide are preferentially active in patients with activated B-cell-like (ABC) DLBCL[12, 13]. Unfortunately, the large phase III studies comparing R-CHOP + ibrutinib or R-CHOP + lenalidomide with standard R-CHOP failed to meet their endpoints. Therefore, both combinations are not available to treat patients with DLBCL.

Antibody-drug conjugates (ADC) represent another novel class of anticancer agents. Polatuzumab vedotin is an ADC comprising a humanized immunoglobulin G1 (IgG1) anti-human CD79b monoclonal antibody and a potent anti-mitotic agent, mono-methyl auristatin E (MMAE). Upon binding to CD79b, polatuzumab-vedotin is internalized and MMAE is released causing cell death[14]. The addition of polatuzumab-vedotin to rituximab and bendamustine in patients with relapsed DLBCL significantly improved median progression-free survival (PFS) (9.5 vs. 3.7 months) and overall survival (OS) (12.4 vs. 4.7 months) in comparison to the combination of rituximab and bendamustine alone[15]. Based on these results, the combination of polatuzumab-vedotin, rituximab, and bendamustine has been approved by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of r/r DLBCL.

The combination of the anti-CD19 antibody tafasitamab and lenalidomide (12 cycles), followed by tafasitamab monotherapy until progression, in transplant ineligible patients with r/r DLBCL resulted in a 57.5% objective response rate, with a median duration of response (DOR) of 43.9 months and median OS of 33.5 months[16, 17]. This combination has also been approved by the FDA and EMA for transplant ineligible patients with r/r DLBCL. However, a real-world study of tafasitamab and lenalidomide in r/r large B-cell lymphoma, with 75 (91%) of patients not meeting the eligibility criteria of the above mentioned clinical trial, showed significantly worse clinical outcomes, including ORR, PFS, and OS, compared to the licensing study[18].

Several bispecific antibodies (BsAbs) have been designed for the treatment of patients with r/r DLBCL. BsAbs combine two different antigen-binding regions from different antibodies to create a single antibody-derived molecule with bispecific antigen binding. BsAbs such as glofitamab or epcoritamab, targeting CD20 and CD3, have demonstrated very promising anti-lymphoma activity in heavily pretreated patients[19, 20] and are approved as monotherapy in third line or later irrespective of a prior CAR-T cell therapy or HDCT/ASCT.

Recent data show that the efficacy of BsAbs is significantly increased when used in combination with conventional chemotherapy or biologicals. The prospective, randomized, phase 3 study STARGLO investigated glofitamab in combination with gemcitabine and oxaliplatin (GemOx) to treat transplant ineligible DLBCL patients in first or later relapses[21]. The ORR of glofitamab-GemOx and R-GemOx were 68.3% and 40.7%, respectively, resulting in a median PFS of 13.8 months with glofitamab-GemOx and 3.6 months after R-GemOx. Most importantly, after a median follow-up of 24.7 months, a significant improvement of OS was observed (median OS not reached and 13.5 months, HR 0.60 [0.42-0.85], p=0.003)[22]. Based on these results EMA approved the combination of glofitamab and GemOx for the treatment of adult patients with relapsed/refractory DLBCL ineligible for HDCT/ASCT in the second line

or later on April 14, 2025. Based on this approval, this regimen is also a therapeutic option for CAR-T naive patients.

2.2. Investigational drug: loncastuximab tesirine

Loncastuximab tesirine is an ADC that consists of a humanized anti-CD19 monoclonal antibody linked to a pyrrolobenzodiazepine (PBD) dimer toxin[23] CD19 is highly expressed in most B-cell malignancies, making it a compelling therapeutic target. In preclinical studies, loncastuximab tesirine demonstrated potent and selective antitumor effects both *in vitro* and *in vivo*, with DNA-PBD crosslinks remaining present for up to 36 hours[23].

2.2.1. Clinical experience with loncastuximab tesirine

A phase I study was conducted to evaluate the safety and efficacy of loncastuximab tesirine in patients with relapsed/refractory non-Hodgkin lymphoma (NHL)[24, 25]. The majority of patients enrolled in the study were diagnosed with DLBCL (71.6%) and had received a median of 3 prior lines of therapy. Patients were administered escalating doses of loncastuximab tesirine (15 µg/kg-200 µg/kg) as intravenous injections every 3 weeks. The optimal dose was determined to be 150 µg/kg, achieving significant antitumor activity without excessive drug accumulation or toxicity. At doses higher than 120 µg/kg, 55% of DLBCL patients demonstrated an objective response. Notably, no significant immunogenicity was observed.

Based on pharmacokinetic data from the phase I trial, the subsequent phase II study of loncastuximab tesirine administered a dose of 150 µg/kg for the first 2 cycles and 75 µg/kg thereafter. The phase II study confirmed the previously encouraging data, leading to the approval of loncastuximab tesirine by the FDA and EMA for patients with relapsed/refractory DLBCL and high-grade B-cell lymphoma (HGBL) after 2 or more lines of systemic therapy[26, 27]. The approval was based on achieving an ORR of 48.3%, with a complete response (CR) rate of 24.1% and a median DOR of 10.3 months[28]. Most responses occurred after the first imaging assessment, which took place after 2 cycles of therapy, with a median time to response of 41 days. The study included patients with relapsed/refractory DLBCL and HGBL after 2 or more multi-agent systemic treatments, and although subgroup analyses were limited by the small sample size, similar responses were observed in high-risk patients, including those with double- and triple-hit lymphoma, primary refractory DLBCL, and transformed DLBCL. Furthermore, 13 patients (9%) who relapsed after CAR-T cell therapy were treated with loncastuximab tesirine and demonstrated an ORR of 46%. These findings demonstrate the efficacy of loncastuximab tesirine in r/r DLBCL and in clinical scenarios where rapid disease control is required.

Regarding safety, all patients experienced treatment-emergent adverse events (TEAEs), with the most common being hematologic AEs, fatigue, nausea, and rash. The most frequent grade

≥ 3 adverse events included neutropenia (26%), thrombocytopenia (18%), and elevated gamma-glutamyl transferase (GGT) levels (16%) without other signs of liver toxicity. Unlike other ADCs, peripheral neuropathy was not a common adverse event. Fluid retention, including pleural effusions (8% all-grade, 2% grade ≥ 3), peripheral edema (19% all-grade, 1% grade ≥ 3), and pericardial effusion (1 case), was observed in the phase I trial[24] and effectively managed with premedication using oral dexamethasone and spironolactone diuretics. Rash was also a common adverse event, primarily occurring in sun-exposed areas (12% with only 1 case of grade 3), leading physicians to recommend avoiding prolonged sun exposure. Importantly, no cases of tumor lysis syndrome (TLS) or tumor flare occurred.

In terms of treatment discontinuation, 23% of patients discontinued loncastuximab tesirine due to TEAEs, while dose delays were generally short-lived (< 1 week)[28], lasting less than one week. Most discontinuations were attributed to grade ≥ 3 elevation of GGT (10%). The discontinuation rate was comparable to that of other novel therapies, including tafasitamab and lenalidomide (22%)[17] and polatuzumab vedotin combined with chemoimmunotherapy (21%)[15]. Notably, the trial in patients with r/r DLBCL did not reveal any specific toxicity concerns for patients aged 65 years or older[28].

Several ongoing clinical studies investigate the efficacy of loncastuximab tesirine in combination with other agents. The LOTIS-5 trial (NCT04384484) evaluates the combination of loncastuximab tesirine and rituximab vs. rituximab and GemOx in r/r DLBCL. Key eligibility criteria included DLBCL, HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements, at least one line of prior systemic therapy and previous HDCT/ASCT or ineligibility for HDCT/ASCT[29]. Approximately 350 patients have been enrolled, 20 patients in the run-in phase. Among the latter patients, an ORR of 80% (16/20) with a CR-rate of 50% (10/20) were reported without new safety signals. With a median follow-up of 10.8 months, median PFS was 8.3 months, the median DOR was 8.0 months for all responders and not reached for CR patients. Response was sustained beyond end of treatment in 5 patients. CAR-T eligibility was not an exclusion criterion in this study[30].

The LOTIS-7 study (NCT04970901) is an ongoing phase 1b, multicenter, multi-arm study investigating the combination of loncastuximab tesirine and glofitamab in patients with r/r B-cell lymphoma including a first (dose escalation) and second part (dose expansion). As of the April 14, 2025, a total of 41 patients with aggressive B-cell lymphoma were treated with at least one cycle of loncastuximab tesirine and were evaluated for safety. 51.2% of patients had received ≥ 2 prior therapies, and 19.5% had failed prior CAR-T cell therapy. The most common grade ≥ 3 TEAE was neutropenia (24.4%). Grade 1/2 cytokine release syndrome (CRS) was reported in 29.3% and 7.3% of patients, respectively. Immune effector cell-associated neurotoxicity syndrome (ICANS) grades 1/2 occurred in 2.4% and 4.9% of patients,

respectively, no grade ≥ 3 events were reported. A preliminary efficacy analysis was conducted in 30 DLBCL patients who received doses of 120 µg/kg or 150 µg/kg of loncastuximab tesirine in combination with glofitamab. Remarkably, the best ORR was 93.3% (28/30) with a CR-rate of 86.7% (26/30). The median DOR was not reached. Among 28 responders, 26 patients remain in CR suggesting that the combination of loncastuximab tesirine and glofitamab can induce long-term remissions in a very high percentage of patients treated[31].

Another ongoing phase 2 study (NCT05672251) investigates the combination of loncastuximab tesirine with the BsAb mosunetuzumab for treatment of r/r DLBCL after at least 1 line of therapy irrespective of eligibility for CAR-T cell or HDCT/ASCT therapy [32].

In a retrospective real-world study (RWS) by Epperla et al., 118 patients with r/r DLBCL who received loncastuximab tesirine monotherapy in third or fourth line after failing second or third line CAR-T were reported[33]. Ninety-five patients received loncastuximab tesirine after second line and 23 patients after third line CAR-T cell therapy. Fourteen patients had undergone HDCT/ASCT prior to CAR-T cell treatment. Patients who received loncastuximab tesirine in third line after failure of CAR-T cells had an ORR of 73% (CR-rate of 34%). With a median follow-up of 8.5 months after the start of loncastuximab tesirine, median DOR, PFS, and OS were not reached. The DOR-, PFS-, and OS-rates at 12 months were 68%, 77%, and 84%, respectively. Patients who received loncastuximab tesirine in fourth line after CAR-T cell failure had an ORR of 78% (CR-rate 17%). With a median follow-up of 13 months, median DOR and PFS were 7.6 and 12.0 months, median OS was not reached. Thus, loncastuximab tesirine monotherapy shows to be an effective treatment in patients with r/r DLBCL after multiple lines of therapy including patients who were resistant to or progressed after CAR-T cell therapies.

2.3. Investigational drug: epcoritamab

Epcoritamab is an immunoglobulin (Ig) G1 bispecific antibody (BsAb) that targets both CD3-positive T-cells and CD20-positive B-cells. Its mode of action involves activating T-cells upon binding to CD3 and simultaneously binding to CD20 on B-cells. This dual binding leads to the release of perforin/granzymes and FAS ligand by the T-cells, resulting in the lysis of the target cells[34]. In *in vitro* studies, epcoritamab demonstrated potent activation and cytotoxic activity of CD4+ and CD8+ T-cells in the presence of CD20-expressing cells, independent of the T-cell receptor specificity[35]. *Ex vivo* studies also showed strong cytotoxicity of epcoritamab against tumor cells derived from patients with DLBCL and follicular lymphoma (FL), regardless of their prior treatment with anti-CD20 monoclonal antibodies (mAbs)[35].

2.3.1. Clinical experience with epcoritamab

In the dose-expansion cohort of a phase I/II study (ClinicalTrials.gov identifier: NCT03625037), adults with relapsed or refractory large B-cell lymphoma and at least two prior therapy lines

(including anti-CD20 therapies) received epcoritamab subcutaneously (sc) in 28-day cycles. The treatment regimen included once weekly step-up doses in weeks 1-3 of cycle 1, followed by full doses once weekly (QW) through cycle 3, once every 2 weeks (Q2W) in cycles 4-9, and once every 4 weeks (Q4W) in cycle 10 and thereafter until disease progression or unacceptable toxicity. The primary endpoint was ORR. A total of 157 patients were treated in the study, with a median age of 64 years (range, 20-83) and a median of three prior therapy lines (range, 2-11). The majority of patients (61.1%) had primary refractory disease, and 38.9% had prior exposure to CAR-T cell therapy. At a median follow-up of 10.7 months, the ORR was 63.1% (95% CI, 55.0 to 70.6), and the CR rate was 38.9% (95% CI, 31.2 to 46.9). Overall and complete response rates were similar across key prespecified subgroups. With a median follow-up of 25.1 months, 64.2% of complete responders remained in CR at 24 months underscoring the curative potential of epcoritamab in patients in CR. Estimated 24-months PFS- and OS-rates among complete responders were 65.1% and 78.2%, respectively, and 27.8% and 44.6% in all patients enrolled[36].

The most common TEAEs observed were CRS in 49.7% of patients (grade 1 or 2: 47.1%; grade 3: 2.5%), pyrexia (23.6%), and fatigue (22.9%). ICANS occurred in 6.4% of patients, including one fatal event[20].

The 1b/2 EPCORE NHL-2 study evaluating 29 patients with r/r DLBCL eligible for HDCT/ASCT also showed promising outcomes. Patients on study received epcoritamab in combination with rituximab, dexamethasone, cytarabine, and oxaliplatin or carboplatin (R-DHAX/C) followed by either consolidative HDCT/ASCT or epcoritamab monotherapy if patients refused HDCT/ASCT. The ORR was 76% and the CR-rate was 69% among all patients. Of patients achieving a CR, 81% remained in CR at 24 months after treatment initiation and 2-year OS was 86%. CRS was mostly low grade (38% grade 1, 7% grade 2), resolved within days, and did not lead to treatment discontinuation. ICANS (grade 2) occurred in 1 patient and led to treatment discontinuation. There were no fatal TEAEs[37]. Similar data are reported for the combination of R-ICE with epcoritamab. In 31 HDCT/ASCT eligible r/r DLBCL patients who had received ≥1 prior line of treatment, ORR was 87%, 20 patients (65%) achieved a CR and 7 (23%) patients a PR (NCT04663347)[38, 39].

In another part of the EPCORE NHL-2 study and similar to the STARGLO study (glofitamab plus GemOx) described above, the combination of epcoritamab with gemcitabine and oxaliplatin was investigated in 103 patients with r/r DLBCL after at least one treatment line. These patients had failed or were ineligible for HDCT/ASCT. Patients had challenging-to-treat disease: 62% of patients were pretreated with ≥ 2 prior treatment lines, 28% had failed CAR-T cell therapy, and 52% of patients suffered from refractory disease. Seventy % of patients were refractory to last therapy before study entry. The ORR and the CR-rate were 85% and

61%, respectively. Median duration of CR and OS were 23.6 and 21.6 months, respectively. Common TEAEs were cytopenias and CRS. CRS was mostly of low grade (52% overall, 1% grade 3), and resolved without discontinuation of study drug. Notably, this study included more patients with ≥ 2 prior lines of treatment (62% vs. 37%) and prior CAR-T cell therapy (28% vs. 7%) as compared to the STARGLO study[21, 40].

Forty patients with r/r DLBCL (median age 72 years) who were ineligible for or had failed HDCT and ASCT prior were treated with fixed duration epcoritamab and lenalidomide after at least one prior line of treatment (NCT05283720). Patients showed an ORR of 67.6% with 51.4% of patients achieving a CR. Consistently high CR-rates were observed across all subgroups, including patients treated second line (56.3%; n=16) and patients who had failed CAR-T cell therapy (50%; n=10). No new safety signals were reported. CRS was observed in 65% of patients (grade 1: 35%; grade 2: 20%; grade 3: 10%). ICANS occurred in one patient only (2.5%; grade 3), and resolved within 3 days[41].

To summarize, epcoritamab in combination with chemotherapy or biological agents demonstrates highly promising efficacy in CAR-T cell pre-treated and CAR-T cell naive as well as in HDCT/ASCT eligible and ineligible r/r DLBCL patients with a favorable safety profile. Importantly, CAR-T eligibility was not an exclusion criterion for the above-mentioned studies.

2.4. Rationale for the study

2.4.1. Rationale for the treatment of CAR-T eligible patients with primary refractory disease/early relapse in second-line

The incorporation of CD19-directed CAR-T therapies has significantly changed the treatment algorithm for patients with aggressive lymphomas. The ZUMA-7 and TRANSFORM studies demonstrated the superiority of second line CAR-T cell therapy over SOC resulting in the approval of CAR-T cells for second line treatment of patients with early relapse or primary refractory disease[8, 9]. Nonetheless, the efficacy and safety of CAR-T cells is far from optimal. In the ZUMA-7 trial, 2-year PFS- and OS-rates of 46% and 60% were reported[42]. In the TRANSFORM study, patients showed PFS- and OS-rates of 50.9% and 62.8% after a median observation time of 3 years[43]. These results were confirmed by various real-world analyses with large patient numbers[44 - 47]. Overall, about half of all patients treated fail CAR-T cell therapy in second line. Importantly, CAR-T cell therapies are also associated with significant toxicities such as CRS (up to 92% all grades, 6% grade ≥ 3), ICANS (up to 61% all grades, 21% grade ≥ 3), and prolonged cytopenias (grade ≥ 3 up to 43%)[8-9, 48-49]. Furthermore, it remains unclear if patients treated with CAR-T cells in second line show better outcomes when compared to patients who receive CAR-T cells as third line treatment. In the ZUMA-7 trial an OS benefit was demonstrated for patients receiving CAR-T cells compared to SOC. However, only 57% of patients in the SOC arm were treated with CAR-T cells after failing SOC. Thus, it

remains unclear if CAR-T cell therapy given second line is superior to a later line CAR-T cell therapy. Real-world analyses suggest that the efficacy of CAR-T cells applied in second line or later does not significantly differ[46-47].

Early signals from phase 1 and 2 studies demonstrate promising efficacy of BsAbs and ADCs. As outlined in detail above, combinations of BsAbs and conventional chemotherapy or various biologicals are more effective compared to BsAbs alone (see chapters 2.2.1 and 2.3.1). Consequently, EMA approved the combination of glofitamab, gemcitabine and oxaliplatin based on the results of the STARGLO study. The approval was granted irrespective if patients are CAR-T cell eligible or received a prior CAR-T cell treatment. Thus, as of today, the combination of glofitamab and GemOx represents a licensed alternative to CAR-T cell therapies in second line.

The safety signals for BsAbs either as single agents or in combination with conventional chemotherapy or biologicals compare - albeit indirectly - favorably to the toxicities of CAR-T cells. In particular, CRS (max. 63% vs. max. 92% following CAR-T cells), ICANS (max. 8% vs. 61% following CAR-T cells), and neutropenia grade ≥ 3 (max. 27% vs. max. 69% following CAR-T cells) do occur significantly less frequent after BsAbs as compared to CAR-T cell therapy, respectively[8, 19, 20, 48].

Internationally, a number of clinical studies enrolling patients with r/r DLBCL after failure of first line therapy are ongoing. These studies investigate the efficacy and toxicity of BsAbs and ADCs in combination with immunochemotherapy and/or biologicals. None of these studies require prior treatment with CAR-T cells.

The study with a design most similar to the CLEAR study is LOTIS-7 (NCT04970901) investigating the combination of loncastuximab tesirine and glofitamab, another CD3xCD20-directed BsAb, in r/r DLBCL, HGBL and FL grade 3B patients. The study is actively recruiting CAR-T cell naive patients in Europe and the USA. Preliminary data show a very promising efficacy and good tolerability (details presented above)[31]. Other studies combine venetoclax, ibrutinib, prednisone, obinutuzumab, revlimid and polatuzumab vedotin (ViPOR-P; NCT04739813), or loncastuximab tesirine and the CD3xCD20-directed BsAb mosunetuzumab for treatment of r/r DLBCL and also do not require the exclusion of patients without prior CAR-T cell therapy or HDCT/ASCT (NCT05672251). The phase 3 SUNMO study (NCT05171647) investigates the efficacy and safety of mosunetuzumab in combination with polatuzumab vedotin in patients with r/r DLBCL, HGBL, transformed FL (trFL) and FL Grade 3B after at least one prior therapy line in comparison with R-GemOx without consideration of CAR-T eligibility. The results of SUNMO study have been recently presented and demonstrated to be very encouraging[50]. Along these lines, the results of the NCT03671018 phase 1b/2 trial treating 120 r/r aggressive B-cell lymphoma patients with mosunetuzumab and polatuzumab vedotin

after at least one prior treatment regimen and irrespective of CAR-T eligibility were published and showed promising results as well[51].

Given the very promising efficacy and safety data from various trials combining BsAbs with other agents, performing a clinical study in r/r DLBCL patients combining epcoritamab and loncastuximab tesirine before patients failed CAR-T cell treatment is scientifically and ethically warranted to further improve outcomes of DLBCL patients. Patients failing study treatment may still be treated with CAR-T cells with results not significantly differing from earlier CAR-T cell therapy.

2.4.2. Rationale for the treatment of CAR-T pretreated patients in third-line

Patients who experience treatment failure after CAR-T cell therapy as second-line treatment represent an unmet medical need, with a historically very poor prognosis and short survival[11]. Therefore, there is a strong need for new strategies to improve the survival outcomes of patients with r/r DLBCL post-CAR-T. As described above, loncastuximab tesirine and epcoritamab have demonstrated significant efficacy as monotherapies following CAR-T cell failure.

Given the individual efficacy and distinct mechanisms of action of loncastuximab tesirine and epcoritamab, both agents appear to be ideal candidates for a combination therapy post-CAR-T as well. Like in CAR-T naive patients, the combination of loncastuximab tesirine and epcoritamab has the potential to improve the ORR as third line therapy after CAR-T cell failure, while maintaining the safety profiles reported for both constructs when administered as single agents. Although loncastuximab tesirine and epcoritamab showed a positive benefit risk balance when investigated individually in phase I/II trials, the efficacy and safety of the combination have not been studied thus far.

2.5. Rationale for the safety and efficacy run-in phases and interim analysis

Data from the phase I-II studies indicate acceptable safety profiles for loncastuximab tesirine and epcoritamab as single agents[20, 28]. In the CLEAR study, two safety analyses will be conducted to address different safety aspects. The first analysis of the dose-limiting toxicities (DLTs), after completing the safety run-in phase, will occur 60 days after 20 patients, irrespective of pretreatment with CAR-T cells, started treatment with loncastuximab tesirine and epcoritamab. These patients will have received at least two cycles of loncastuximab tesirine and one cycle of epcoritamab. This analysis will enable a first detailed analysis of all AEs, particularly focusing on DLTs and severe AEs, such as CRS, ICANS, macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), TLS, infections, liver and skin toxicity, and edema/effusion. The observed AEs will be compared to those experienced in the loncastuximab tesirine phase II and epcoritamab phase I/II studies[20, 28].

The findings will be submitted to the Clinical Trial Information System (CTIS) as part of a substantial modification for review and decision-making on the continuation of the study.

The Data Safety Monitoring Committee (DSMC) will finally assess all available safety and tolerability data and decide whether the recommended doses are associated with acceptable safety and tolerability, comparing the adverse events observed in the combination therapy with those observed when each drug was used individually as well as other available evidence. DSMC shall make recommendations regarding the trial design including the recommendation to stop the trial. For legal and ethical reasons, the sponsor shall follow DSMC recommendations, with very few exceptions.

Special attention will be given to the severity and frequency of AEs observed with loncastuximab tesirine and epcoritamab as monotherapies, as well as the occurrence of any new AEs not previously described for either drug. Once the principal investigator and the DSMC have confirmed the dose with acceptable safety and tolerability of loncastuximab tesirine and epcoritamab, the study will continue at the defined dose level. For both agents the doses approved according to the Summary of Product Characteristics (SmPC) are not allowed to be exceeded (i.e. 150 µg/kg for loncastuximab tesirine and 48 mg for epcoritamab). Based on the observed safety results of the safety run-in phase, the dose of loncastuximab tesirine can be decreased to the level -1 (75 µg/kg) or the total number of the loncastuximab tesirine administrations can be reduced to a fixed dose, if required.

For the group of patients not pretreated with CAR-T cells, an additional and separate efficacy analysis is planned after the 20th CAR-T naive patient started treatment with loncastuximab tesirine and epcoritamab and had a second response assessment (12 weeks after treatment start) by FDG-PET/CT (-/MRI). The primary endpoint of the CLEAR study is BORR. Studies with CAR-T cells in second line, namely the ZUMA-7 (n=180) and TRANSFORM (n=92) studies, demonstrated an ORR of 83% and 87% respectively. Thus, the pooled ORR being 84% with a 95% CI of 79-88%[8, 9]. For this study, a BORR < 60% is considered not acceptable. The BORR will be reported to the DSMC, the members of which will meet to evaluate the efficacy of study drugs in the first 20 CAR-T naive patients included in the study. The results of the efficacy evaluation by the members of the DSMC will be communicated and discussed with the principal investigator, the study committee, and the sponsor of the study. The final recommendation to continue, modify or stop the study lies with the DSMC. These data will be submitted to CTIS as well as part of a substantial modification for review and decision-making on the continuation of the study. If the BORR is < 60% the study will be terminated early for CAR-T naive patients. The study sponsor will follow the DSMC’s suggestion to continue or stop the study.

An interim analysis will be conducted 6 months after 50th patient has been recruited, irrespective of pretreatment with CAR-T cells. Regarding efficacy, the study will proceed only if after 50 these patients the (B)ORR exceeds 60%. If the (B)ORR is 60% or lower, the study may be terminated. In the event of AEs occurring in individual patients that have not been observed previously, or if known AEs of loncastuximab tesirine and epcoritamab occur more frequently or are more severe than expected, the dosing of loncastuximab tesirine and/or epcoritamab will be modified, considering the observed adverse events (e.g., severe CRS, ICANS vs. increased GGT, edema, etc.). The data of the interim analysis will be submitted to the CTIS as part of a substantial modification for review and decision-making on the continuation of the study. The DSMC will evaluate the efficacy and safety profile of the combination of epcoritamab and loncastuximab tesirine and the protocol adherence and decide on the continuation of the study.

2.6. Risk-Benefit considerations

Currently, more than 50% of patients with r/r DLBCL do not achieve remission with standard second-line salvage therapies. These patients are left with limited treatment options, including highly toxic alternative therapies or palliative care, with poor expectations for long-term remissions and survival. Previous analyses have shown that patients who fail second-line therapy have long-term OS rates of less than 20% after 2 years[2, 10]. The prognosis is even worse for patients who progress or relapse after CAR-T cell treatment, with a median OS of around 5 months only[11]. Therefore, there is an urgent need to optimize therapy for relapsed/refractory aggressive B-cell lymphoma.

The individual efficacy of loncastuximab tesirine and epcoritamab as monotherapies in patients with r/r aggressive B-cell lymphoma is highly promising[20, 28]. Combining loncastuximab tesirine and epcoritamab is expected to further enhance their efficacy. The most frequent adverse events associated with loncastuximab tesirine (skin reactions, GGT, edema, and effusion) and epcoritamab (CRS, pyrexia, infections) were shown to be manageable. Both study agents are associated with hematological toxicity. In regard to thrombocytopenia, an additive effect cannot be excluded, however such events could be easily handled via transfusion of platelets. An additive effect cannot be excluded for neutropenia as well. In general, such events are also common for current standard of care (SOC) options outside the study, which are even more toxic. With regard to hematological toxicities the protocol suggests to consider precautions and prophylaxis as presented in the chapters 8 and 9. Although it is not anticipated that individual AEs will significantly interfere, all AEs occurring in patients on study, particularly those typically associated with loncastuximab tesirine and/or epcoritamab, will be closely monitored and managed according to a predefined program to ensure safety and minimize patient risks. The safety run-in phase of the study in particular aims to assess

the safety of the combination of loncastuximab tesirine and epcoritamab. Additionally, an efficacy run-in phase for CAR-T naive patients will be performed to avoid undertreatment in this patient cohort. Based on current knowledge of the clinical pharmacology and metabolism of loncastuximab tesirine and epcoritamab, the potential for clinically relevant drug-drug interactions is considered to be low. The safety and feasibility of the combination therapy will be closely monitored and evaluated at the end of the safety run-in phase by an independent Data Safety Monitoring Committee.

3. OBJECTIVES

3.1. Primary objective

The primary objective of this study is:

- to estimate the best overall response rate (BORR), including complete and partial remissions, achieved up to 12-months of treatment with loncastuximab tesirine and epcoritamab in patients with r/r DLBCL, HGBL and FL grade 3B who have either failed first-line therapy administered at least one time and are CAR-T naive or have failed CAR-T cell therapy as a second-line treatment.

3.2. Secondary objectives

Secondary objectives for efficacy are

- Progression-free survival (PFS)
- Overall survival (OS)
- Complete remission (CR) rate
- Partial remission (PR) rate
- Time to complete response
- Time to best response
- Duration of response
- Progression rate
- Rate of relapse
- Outcome according to biological characteristics of the lymphoma

Secondary objectives to evaluate the safety and tolerability of trial medication are

- Rate of treatment-related deaths
- Safety and tolerability, and protocol adherence of loncastuximab tesirine when combined with epcoritamab

4. ENDPOINTS

4.1. Primary endpoint

- The primary efficacy endpoint is the BORR defined as the proportion of patients with r/r DLBCL, HGBL and FL grade 3B who achieve a complete or partial remission as best response up to 12-months of study treatment according to the 2014 Lugano criteria, as assessed by local investigator review.

4.2. Secondary endpoints for efficacy

- 2-year progression-free survival (PFS) with a 95% confidence interval. PFS is defined as time from the first dose of study drug until one of the following events occurs, whichever is first:

- Disease progression
- Relapse
- Death due to any cause

Patients who have not experienced an event at the time of analysis will be censored at the most recent date of disease assessment.

- 2-year overall survival (OS) defined as the time from the first dose of study drug to death of any cause. Patients who have not experienced an event at the time of analysis will be censored at the last date known to be alive.
- Complete response (CR) rate measured as the number of complete remissions as best response (achieved up to 12 months) divided by the number of patients treated with at least one dose of study drug.
- Partial response (PR) rate measured as the number of partial remissions as best response (achieved up to 12 months) divided by the number of patients treated with at least one dose of study drug.
- Time to complete response measured as the time from the start of therapy to documentation of complete remission.
- Time to best response (achieved up to 12 months) measured as the time from the start of therapy to documentation of the best tumor response according to type of response.
- Duration of response measured as the time from documentation of tumor response (complete or partial remission) to relapse or progressive disease.
- Progression rate measured as the number of progressions (observed up to 12 months) divided by the number of patients treated with at least one dose of study drug.
- Relapse rate measured as the number of relapses divided by the number of patients included with complete or partial remission.
- Outcomes according to biological characteristics of the lymphoma (see Section 4.5).

Response assessment will be done according to the Lugano Classification (please refer to 11.7.4)

4.3. Secondary endpoints for safety and tolerability

Secondary endpoints for safety and tolerability are

- AEs (see Section 13.1)
- SAEs (see Section 13.2)
- Rate of treatment-related deaths defined as the number of treatment-related deaths during therapy or up to 2 months after the end of therapy divided by the number of patients treated with at least one dose of study drug.

4.4. Secondary endpoints for protocol adherence

Secondary endpoints for protocol adherence are

- Number of treatment cycles received
- Duration of treatment cycles
- Cumulative doses of loncastuximab tesirine and epcoritamab

4.5. Secondary endpoints for outcomes according to lymphoma biology

Lymphoma tissue from all patients will undergo characterization through morphology, immunohistochemistry, and FISH. The molecular DLBCL subtype will be determined using the cell of origin classification, as well as the translocation status of *BCL2* and *MYC*. Gene expression profiling and targeted resequencing will be conducted to identify mutations associated with resistance or sensitivity to the combination of loncastuximab tesirine and epcoritamab. The DLBCL molecular subtypes (activated B-cell type [ABC], germinal-center B-cell type [GCB], unclassified DLBCL) will be assessed using the NanoString platform. Biomarker and minimal residual disease assessments will be performed to identify potential predictive markers for treatment outcomes. Additional biomarker analyses in tumor tissue and/or blood will provide insights into the mechanism of action of loncastuximab tesirine and epcoritamab, as well as the underlying biology of the disease.

5. TRIAL DESIGN AND HYPOTHESIS

This is a prospective, multicenter, single-arm, open-label, phase II study designed to evaluate the toxicity and efficacy of the combination of loncastuximab tesirine and epcoritamab in about 114 evaluable patients with relapsed/refractory aggressive B-cell lymphoma (DLBCL, HGBL or FL grade 3B). CAR-T cell naive patients who have failed first-line therapy and patients who

have received CAR-T cells as second-line therapy and experienced CAR-T failure will be eligible for inclusion.

The study will consist of a safety run-in phase to identify early and unexpected AEs associated with the combination therapy, irrespective of CAR-T pretreated status, followed by a treatment phase comprising a maximum of 6 cycles of loncastuximab tesirine administered every 21 days, combined with epcoritamab administered every 28 days up to one year (a maximum of 13 cycles). After completion of the combination therapy and ninth cycle of epcoritamab, consolidation therapy with epcoritamab alone will continue up to a total of one year from the initiation of epcoritamab (a maximum of 13 cycle) or until disease progression or relapse, unacceptable toxicity, death, major protocol deviation, pregnancy, or patient/investigator decision whichever occurs first. For CAR-T naive patients, an early efficacy assessment is planned after the 20th patient started treatment with loncastuximab tesirine and epcoritamab and had a second response assessment (12 weeks after treatment start) by FDG-PET/CT (-/MRI).

An independent DSMC will regularly review the safety and efficacy data and provide recommendations for the ongoing conduct of the study. The hypothesis is that the combination of loncastuximab tesirine and epcoritamab will achieve an overall response rate (complete response and partial response) of at least 75%, thereby improving the efficacy of both drugs when given individually, as well as improving standard rituximab-chemotherapy combinations used as salvage therapy in patients with r/r DLBCL, HGBL or FL grade 3B as second-line treatment. In patients who have experienced CAR-T cell failure and require third-line therapy the dismal prognosis of third-line therapy shall be improved.

5.1. Study duration

With an anticipated recruitment rate of 80 patients per year, the enrollment for the loncastuximab tesirine/epcoritamab combination study is projected to be completed within eighteen months from the initiation of all study centers. Following the nine-month induction period, a consolidation phase with epcoritamab monotherapy will continue for every patient up to a total of one year from the initiation of epcoritamab (a maximum of 13 cycle epcoritamab) or until disease progression or relapse, unacceptable safety and tolerability, death, major protocol deviation, pregnancy, patient or investigator decision whichever occurs first. After end of treatment, a patient remains in the follow-up until the end of the study. The study will end 3 years after the last patient enrolled in the study. Consequently, the study is expected to close 4.5 years after the commencement of recruitment.

6. STUDY SITE AND STUDY POPULATION

6.1. Requirements for participating investigators and study sites

Participating investigators and trial sites must meet specific criteria to ensure their expertise and experience in treating patients with DLBCL, as well as their adherence to Good Clinical Practice (GCP) guidelines and conducting clinical trials. The selection of participating institutions will be based on previous recruitment into studies of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL)/German Lymphoma Alliance (GLA) or Italian Study Group Fondazione Italiana Linfomi (FIL) studies. Regular attendance of study group meetings and other group activities will be considered in the selection process.

6.2. Trial sites and number of trial subjects

A maximum of 38 institutions will be involved in the trial, with three of them being active members of FIL. The trial master file will contain an up-to-date list of all participating centers. A total of 120 patients, aged 18 years or older, with histologically confirmed DLBCL, HGBL or FL grade 3B at the time of relapse or disease progression, will be recruited. If any patients do not receive any study medication, they will be replaced.

6.3. Selection of the trial subjects

All relapsed/refractory patients with confirmed DLBCL, HGBL or FL grade 3B and at least 18 years of age presenting at each of the participating centers are eligible if the following criteria are met.

6.3.1. Inclusion criteria

Disease:

1. Subjects with histologically confirmed relapsed/refractory DLBCL based on pathology report (WHO 2022 criteria)
   a. DLBCL (*de novo* or transformed)
   b. High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
   c. High-grade B-cell lymphoma, not otherwise specified (NOS)
   d. Follicular lymphoma grade 3B

   Diagnostic biopsy performed at the time of relapse/progressive disease no longer than 3 months before study entry must be available, with sufficient material for central review and complimentary scientific analyses. CD20 expression (or a high likelihood of CD20 expression) based on immunohistochemistry should be documented prior enrollment into the study.

Refractory disease is defined as no remission to the last therapy. Subjects intolerant to previous therapy are excluded. Two groups of patients are eligible:

- Progressive disease (PD) or stable disease (SD) as best response to previous therapy.
- Complete (CR) or partial response (PR) as the best response after previous therapy, with biopsy-proven relapse occurring < 6 months after end of treatment.

Relapsed disease is defined as subjects achieving complete or partial remission to previous therapy, followed by biopsy-proven relapse ≥6 months after treatment completion. Subjects with refractory and early relapsed (≤12 months) disease after first line anti-CD20-/anthracycline-containing therapy are eligible. Subjects with late relapsed (>12 months) disease after first line anti-CD20-/anthracycline-containing therapy can be enrolled in the study if deemed ineligible to high dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) or if refuse to undergo HDCT/ASCT. Subjects relapsed/refractory to second line CAR-T cell therapy are eligible.

2. Subject must be 18 years or older.
3. Subject must be eligible to receive and in need of treatment initiation based on symptoms and/or disease burden, as assessed by the investigator.
4. Eastern Cooperative Oncology Group Performance (ECOG) status 0-2.
5. Subject must have one or more measurable disease sites defined as follows:
    a. A positron emission tomography/computed tomography (PET/CT) scan demonstrating PET- positive lesion(s) AND
    b. At least one measurable nodal lesion (long axis > 1.5 cm and short axis > 1.0 cm) or ≥ one measurable extra-nodal lesion (long axis > 1.0 cm) on CT scan or MRI.
6. Ability to understand and willingness to sign written informed consent. Signed informed consent must be obtained before any study specific procedure.

Contraception:

7. Women of childbearing potential and sexually active men must practice a highly effective method of birth control during and after the study, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. 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 giving informed consent until at least 7 months after the patient receives his last dose of study treatment. Men must agree not to donate sperm from the time of giving informed consent until at least 7 months after the patient receives his last dose of study treatment. For female subjects, they apply for 12 months after the last dose of the study drug. A woman is considered to be of childbearing potential until becoming post-menopausal or permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Post-menopausal status is defined as no menstrual periods for a continuous 12-month period without an alternative medical cause. A post-menopausal state can be confirmed by a high follicle-stimulating hormone (FSH) level within the postmenopausal range, especially in women not using hormonal contraception or replacement therapy. The investigator or a designated associate will provide guidance to patients on achieving highly effective contraception (with a failure rate of less than 1%), such as intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal occlusion, having a vasectomized partner, or sexual abstinence. Male patients are required to use condoms unless their female partner is permanently sterile.
8. Women of childbearing potential participating in the study will be required to undergo a pregnancy test using either urine or serum beta-human chorionic gonadotropin (beta-hCG) at the screening visit. A negative result is necessary for inclusion in the study.

Adequate baseline organ function tests collected no more than 7 days before starting study treatment:

9. Total bilirubin ≤ 1.5 times the upper limit of normal (ULN), except for patients with Gilbert syndrome, cholestasis due to hepatic hilum adenopathies or liver involvement, or biliary obstruction due to lymphoma, who may have a total bilirubin ≤ 3 times the ULN.
10. ALT and AST and GGT ≤ 2.5 times the ULN, or ≤ 5 times the ULN for patients with liver involvement by lymphoma.
11. Glomerular filtration rate (GFR) ≥ 45 mL/min/1.73 m² according to the CKD-EPI formula. If not initially within target range, this evaluation may be repeated after at least 24 hours, either using the CKD-EPI formula or by 24-hour sampling. If the subsequent result is within the acceptable range, it may be used to fulfill the inclusion criteria.
12. Prothrombin time/INR/aPTT ≤ 1.5 times the ULN, unless the patient is receiving anticoagulation (although the INR should not exceed 4.0).

13. Platelet count ≥ 75,000/mm³ without transfusion in the prior 7 days.
14. Hemoglobin ≥ 8 g/dL.
15. Absolute neutrophil count ≥ 1,000/mm3 (off growth factors at least 72 hours).
16. Left ventricular ejection fraction > 45%.

Concomitant Medications:

17. Subjects should not be taking any active medication known to decrease T-cell numbers or activity, or any other concurrent immunosuppressive medication, except for up to 10 mg of prednisone daily or an equivalent dose, unless it is necessary for disease control during the screening period, premedication and/or CRS/ICANS management within the study.
18. Subjects must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of the study drug, nor be currently enrolled in another interventional clinical study or have been previously enrolled in this study, unless the agent being used has been approved under emergency authorization (e.g., anti-SARS-CoV-2 monoclonal antibodies).
19. Acute toxicity (except alopecia, fatigue) of any prior lymphoma therapy should be resolved to Grade ≤ 1 (with the exception of prior CRS or ICANS that should be fully resolved) at study screening.
20. The subject should not have received vaccination with live-attenuated vaccines within 28 days prior to screening, and they should not be expected to require any live-attenuated vaccination during their participation in the study, including at least 3 months following the last dose of study treatment. However, vaccination with coronavirus mRNA and adenovirus-based vaccines, which are not live-attenuated vaccines, is permitted.

6.3.2. Exclusion criteria

Patients who meet any of the following criteria at the time of screening will be excluded:

1. Any prior lymphoma-directed treatment, except for first-line anti-CD20-/anthracycline-containing chemoimmunotherapy or second line CAR-T cell therapy. Particularly, patients previously treated with loncastuximab tesirine and any CD3xCD20 bispecific antibody therapy are not eligible.
2. Patients with late relapse (>12 months) after first-line immunochemotherapy considered HDCT/ASCT eligible as assessed by the local investigator.
3. Known central nervous system (CNS) involvement.
4. Diagnosed or treated for any malignancy other than r/r DLBCL, HGBL or FL grade 3B within the last 3 years, except for adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, non-invasive basal cell or squamous cell skin carcinoma, adequately treated carcinoma *in situ* without evidence of disease, localized prostate cancer, post-radical prostatectomy with non-rising prostate-specific antigen levels < 0.1 ng/mL, cervical carcinoma of stage 1B or less, non-invasive, superficial bladder cancer or any curable cancer with a CR of > 2 years duration.
5. Known history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or active hepatitis B virus (HBV) infection or any known active systemic bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds). Patients with serologic markers of HBV immunization due to vaccination (HBsAg negative, Anti-HBc negative, and Anti-HBs positive) will be eligible. Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
6. CMV-PCR positive at baseline.
7. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or interfere with the feasibility to administer study drugs including active hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), history of cutaneous collagenous vasculopathy and capillary leak syndrome.
8. Concurrent treatment with another investigational agent or radiation therapy.
9. Any psychological, cognitive, familial, or social condition that, in the investigator's opinion, compromises the patient's ability to understand the patient information, give informed consent, or comply with the study protocol.
10. Participation in another clinical trial.
11. Known history of hypersensitivity and/or positive serum human anti-drug antibody (ADA) against any component of the study products or of the concomintant medication or an anti-CD19 antibody.

12. History of Stevens-Johnson syndrome or toxic epidermal necrolysis.
13. Clinically significant third space fluid accumulation, such as ascites requiring drainage or pleural effusion that either requires drainage or is associated with shortness of breath; or history of pericardial effusion.
14. Pregnancy or breastfeeding.
15. Use of any other experimental medication within 30 days or 5 half-lives prior to the start of the study drug (Cycle 1 Day 1).
16. Close affiliation with the investigational site, such as being a close relative of the investigator or dependent person (e.g., employee or student of the investigational site).

Excluded medical conditions:

17. Congestive heart failure > New York Heart Association (NYHA) class 2.
18. Unstable angina (angina symptoms at rest) or new-onset angina (begun within the last 3 months).
19. Uncontrolled atrial or ventricular cardiac arrhythmia.
20. Left ventricular ejection fraction ≤ 45%.
21. Electrocardiographic evidence of acute ischemia, coronary angioplasty, or myocardial infarction within 6 months prior to screening.
22. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within 3 months before the start of study medication.
23. Congenital long QT syndrome or a QTcF interval of > 480 ms at screening (unless secondary to pacemaker or bundle branch block).
24. Severe chronic pulmonary disease.
25. Known clinically significant liver disease, including hepatitis, current alcohol abuse, or cirrhosis.
26. Autoimmune disease requiring immunosuppressive therapy, except for up to 10 mg prednisone daily (or equivalent).
27. Seizure disorder requiring therapy within the past 12 months. Subjects with a history of seizure disorder beyond must have a complete CNS workup.
28. Major surgery within 4 weeks of the first dose of study drugs, except for lymphoma reasons.
29. Any other co-existing medical or psychological condition that will preclude participation in the study or compromise the ability to give informed consent.

6.3.3 Rationale for gender distribution

All patients who meet the inclusion criteria and do not meet any of the exclusion criteria will be eligible for the study, regardless of gender.

7. PATIENT INCLUSION AND REGISTRATION

Each patient's eligibility will be verified during a screening visit (see Sections 6.3.1, 6.3.2 and 11.1). Informed consent must be obtained prior to any clinical procedures that are performed solely for study-related purposes. After screening, registration will be performed using the electronic case report form (eCRF).

Registration is a web-based procedure. Access to the registration tool is provided to each center at its initiation. Data of an eligible patient are entered. After a check of data consistency, the patient will be enrolled and the investigator is informed about the successful registration immediately via E-mail.

7.1. Information required for registration

- Name of investigator
- Name of pathologist who rendered the diagnosis of DLBCL
- Name of reference pathologist
- Name of nuclear medicine specialist
- Name of radiologist
- Age
- Gender
- Histopathologic report (WHO classification 2022)
- Confirmation that patient conforms to eligibility criteria
- Confirmation that no exclusion criteria apply
- Informed consent form signed and dated by the patient’s own hand

Each subject will be assigned to an individual patient number within the trial, which will be used for pseudonymization of any patient-specific communication within the trial.

8. PRIOR AND CONCOMITANT THERAPY/MEDICATION

8.1. Previous therapy/medication of other indications than the study specific illness

Concomitant therapies include any prescribed medications or over-the-counter preparations used by a patient between the 7 days preceding the study entry and 28 days after the end of study visit. All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

8.2. Generally prohibited therapy/concomitant medication

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy

- Radiotherapy
- Immunotherapy/targeted (other than loncastuximab tesirine/epcoritamab)
- Hormone therapy (other than contraceptives, hormone-replacement therapy or megestrol acetate)

EXCEPTION:

- Hormonal therapy (e.g., GnRH-agonists) for egg cell harvest/fertility preservation prior to registration is allowed in women of childbearing age
- Autoimmune disease requiring immunosuppressive therapy up to 10 mg prednisone daily (or equivalent)

8.3. Loncastuximab tesirine premedication

All loncastuximab tesirine intravenous infusions (21-days cycle) should be administered after premedication containing the following substances:

Cycle 1-6,

Day 0:

- Dexamethasone 4 mg iv or oral (one in the morning and one in the evening)*

Day 1:

- Dexamethasone 4 mg iv or oral (one in the morning and one in the evening)*

If the patient did not receive dexamethasone the day before Day 1 loncastuximab tesirine administration, then dexamethasone must be given at least 2 hours before loncastuximab tesirine administration on the Day 1.

Day 2:

- Dexamethasone 4 mg iv or oral (one in the morning and one in the evening)*

* On days when dexamethasone given to ameliorate epcoritamab side effects overlap with on days when dexamethasone is applied for loncastuximab tesirine, the dose of dexamethasone prescribed to ameliorate epcoritamab toxicity should be used and administered prior to loncastuximab tesirine but not later than 120 minutes prior to subsequent epcoritamab dose (see Section 8.4). If the latter does not apply, 4 mg dexamethasone should be given additionally 30 minutes prior to epcoritamab.

8.4. Epcoritamab premedication

Epcoritamab will be initiated 7 days after the first dose of loncastuximab tesirine to avoid the occurrence of tumor-lysis syndrome. Epcoritamab subcutaneous injections (28-days cycle) should be administered after premedication containing the following substances:

Cycle 1 Day 1, priming dose, and repriming cycle (if applicable):

- Paracetamol 1000 mg oral (administered 30-120 min prior to epcoritamab)
- Clemastin 2 mg iv or oral (or equivalent) (administered 30-120 min prior to epcoritamab)
- Dexamethasone 15 mg iv or oral (or 100 mg prednisone iv or oral) (administered 30-120 min prior to epcoritamab)**

Cycle 1 Days 2-4 and repriming cycle (if applicable):

- Dexamethasone 15 mg iv or oral (or 100 mg prednisone iv or oral)

Cycle 1 Day 8, intermediate dose, and repriming cycle (if applicable):

- Paracetamol 1000 mg oral (administered at least 30 min prior to epcoritamab)
- Clemastin 2 mg iv or oral (or equivalent) (administered 30-120 min prior to epcoritamab)
- Dexamethasone 15 mg iv or oral (or 100 mg prednisone iv or oral) (administered 30-120 min prior to epcoritamab)**

Cycle 1 Days 9-11 and repriming cycle (if applicable):

- Dexamethasone 15 mg iv or oral (or 100 mg prednisone iv or oral)

Cycle 1 Day 15 and repriming cycle (if applicable), first full dose:

- Paracetamol 1000 mg oral (administered 30-120 min prior to epcoritamab)
- Clemastin 2 mg iv or oral (or equivalent) (administered 30-120 min prior to epcoritamab)
- Dexamethasone 15 mg iv or oral (or 100 mg prednisone iv or oral) (administered 30-120 min prior to epcoritamab)**

Cycle 1 Days 16-18 and repriming cycle (if applicable):

- Dexamethasone 15 mg iv or oral (or 100 mg prednisone iv or oral)

Cycle 1 Day 22, second full dose, and repriming cycle (if applicable):

- Paracetamol 1000 mg oral optional

- Clemastin 2 mg iv or oral (or equivalent), optional
- Dexamethasone 15 mg iv or oral (or 100 mg prednisone iv or oral)

  (administered 30-120 min prior to epcoritamab)

Cycle 1 Days 23-26 and repriming cycle (if applicable):

- Dexamethasone 15 mg iv or oral (or 100 mg prednisone iv or oral)

Subsequent epcoritamab applications (cycle 2+):

Patients who experienced grade 2 or 3 CRS[a] following previous dose (cycle 2+):

- Dexamethasone 15 mg iv or oral (or 100 mg prednisone iv or oral)

  (administered 30-120 min prior to epcoritamab)**, on day of epcoritamab application and for three consecutive days following the next administration of epcoritamab until epcoritamab is given without subsequent CRS of grade 2 or higher

Patients without grade 2 or 3 CRS [a] following previous dose (cycle 2+):

- Dexamethasone 15 mg iv or oral (or 100 mg prednisone iv or oral)

  optional, only on day of epcoritamab application

**On days when corticosteroid is administered to alleviate both loncastuximab tesirine and epcoritamab toxicity, it should be given prior to loncastuximab tesirine. The administration should occur within 120 minutes before the subsequent epcoritamab dose. If it is not feasible to administer corticosteroid within that timeframe, an additional 4 mg of dexamethasone should be given 30 minutes prior to epcoritamab. [a]Patients will be permanently discontinued from the study after grade 4 CRS.

For epcoritamab administration beyond the fourth dose (second full dose), the use of corticosteroids for prophylaxis against CRS is optional. However, if CRS grade 2 or higher occurs, CRS prophylaxis should continue until an epcoritamab dose is given without subsequent CRS. On days when both epcoritamab and loncastuximab tesirine are administered, the corticosteroid dose specified in the epcoritamab regimen can serve as the corticosteroid premedication for loncastuximab tesirine.

8.5. Other concomitant therapy/antibiotic prophylaxis

The use of rasburicase for prophylaxis and treatment of tumor lysis syndrome, as well as the prevention of hyperuricemia, is allowed as per institutional guidelines (refer to Appendix G for

tumor lysis syndrome prophylaxis). Subjects with a history of allergic reactions or significant sensitivity to oral uric acid reducing agents (e.g., xanthine oxidase inhibitors and rasburicase) and subjects with known glucose-6-phosphate dehydrogenase (G6PD) deficiency shall be carefully monitored for tumor lysis syndrome. Due to the expected median age > 60 and experience with previous treatment, the probability of undiagnosed G6PD deficiency at study inclusion is deemed very low. Thus, a screening test is recommended only in cases when G6PD deficiency is suspected.

Infectious prophylaxis with aciclovir (2 x 400mg/day) and cotrimoxazole (2 x 960mg twice a week or 3 x 960mg per week) is mandatory for study patients. Levofloxacin 500 mg/day is recommended during the first cycle of epcoritamab due to the high cumulative dose of steroids (1600 mg prednisone or 240 mg dexamethason in total).

Immunoglobulin replacement therapy (IgRT) is recommended for patients with IgG levels below 4 g/l and recurrent or severe infections.

Primary prophylaxis with granulocyte colony-stimulating factors (G-CSFs) is mandatory during cycles 2-4 of loncastuximab tesirine following simultaneous weekly administration of epcoritamab within this phase and is recommented if the absolute neutrophil count (ANC) decreases below 1,000/mm^3 at any other time points.

8.6. Concomitant medications to be used with caution

8.6.1. CYP3A-sensitive substrates with narrow therapeutic index with respect to co-administration with epcoritamab

The potential for epcoritamab to affect the activity of CYP metabolizing enzymes, specifically CYP3A4, is unknown. Therefore, patients should be carefully monitored for potential toxicities when epcoritamab is used concomitantly with medications that are substrates of CYP3A4 and have a narrow therapeutic index:

alfentanil, aprepitant, astemizole, budesonide, buspirone, cisapride, cyclosporine, dasatinib, darifenacin, darunavir, dihydroergotamine, dronedarone, eletriptan, eplerenone everolimus, ergotamine, felodipine, fentanyl, fluticasone, indinavir, quetiapine, conivaptan, lovastatin, lopinavir, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil.

If necessary, doses for CYP3A4 substrates should be adjusted per label recommendations.

8.7. Birth control, breast feeding and fertility

Based on animal studies, loncastuximab tesirine has the potential to cause harm to the embryo and fetus. Therefore, loncastuximab tesirine should not be used during pregnancy. The impact

of epcoritamab on pregnancy is unknown as there are no available clinical data. To ensure the safety of female patients, loncastuximab tesirine and epcoritamab should not be used during pregnancy or in women of childbearing potential who are not using contraception. All females of childbearing potential will undergo a pregnancy test at screening, which will be repeated prior to every treatment cycle.

Female patients can be considered to have no childbearing potential if they are permanently sterile (e.g., through hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or if they are post-menopausal, defined as having no menstrual periods for 12 consecutive months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Women of childbearing potential 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 giving informed consent until at least 7 months after the patient receives his last dose of study treatment. Men must agree not to donate sperm from the time of giving informed consent until at least 7 months after the patient receives his last dose of study treatment. It is currently unknown if loncastuximab tesirine and/or epcoritamab affect the effectiveness of hormonal contraceptives. Therefore, if hormonal contraceptives are used, a barrier method of contraception, such as condoms, must also be employed.

According to the "Recommendations related to contraception and pregnancy testing in clinical trials" provided by the Clinical Trial Facilitation Group (2020-09-21), highly effective birth control methods may include, but are not limited to, the following options [additional details of recommended methods can be provided]:

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation*:
  - Oral
  - Intravaginal
  - Transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation*:
- Injectable
- Implantable
- Intrauterine device
- Intrauterine hormone-releasing system

- Vasectomized partner (with confirmed surgical success)
- Total sexual abstinence (when this is consistent with the preferred and usual lifestyle of the subject). 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.

* Hormonal contraception may be susceptible to interaction with the investigational medicinal product (IMP), which could potentially reduce the efficacy of the contraception method. Therefore, women using hormonal contraceptives should also use a barrier method as a second form of contraception for added protection.

Regarding breastfeeding, it is currently unknown whether loncastuximab tesirine and/or epcoritamab and their metabolites are excreted in human milk. Due to the potential risk to newborns/infants, breastfeeding should be discontinued during treatment with loncastuximab tesirine and/or epcoritamab for at least 3 months and 4 months after the last dose, respectively. Based on the results from animal studies, loncastuximab tesirine may impair male fertility. Therefore, men being treated should be advised to consider having sperm samples preserved and stored before initiating treatment.

9. STUDY TREATMENT ACCORDING TO PROTOCOL

The study consists of four phases: an induction treatment phase, a consolidation treatment phase, a follow-up phase, and a survival follow-up phase.
During the induction treatment phase, patients will receive a maximum of six 21-day cycles of loncastuximab tesirine and nine 28-day cycles of epcoritamab. Following induction therapy, patients who achieve at least a partial remission will proceed to the consolidation treatment phase with epcoritamab up to one year from the initiation of epcoritamab. In the consolidation phase, patients will receive epcoritamab monotherapy administered subcutaneously every 4 weeks (cycles 10-13).
Patients who do not achieve at least a partial remission after induction therapy will discontinue study treatment and enter the follow-up phase. These patients may receive salvage therapy based on the investigator's discretion. Patients who experience disease progression during study treatment or during follow-up will enter the survival follow-up phase, which will continue until the end of the study. These patients may also receive salvage therapy as per institutional standards.

9.1. Pre-phase treatment

Pre-phase treatment, which is a standard procedure and not specific to the study, can be administered before study enrollment. It is at the discretion of the local investigator to decide

whether to administer pre-phase therapy, and it is not mandatory for this study. However, if pre-phase therapy is given, adequate hydration of patients should be ensured, and allopurinol should be administered prior to the start of pre-phase treatment to prevent hyperuricemia. To prevent tumor lysis syndrome, loncastuximab tesirine will be initiated intravenously 7 days prior to the initiation of epcoritamab. Following classification of the expert TLS panel consensus (Cairo et al., Br J Haematol, 2010) can support the assessment of tumor lysis risk:

- LDH < 2 x ULN *and* normal renal function: low-risk
- LDH < 2 x ULN *and* impaired renal function; LDH > 2 x ULN *without* bulky disease *nor* electrolyte disturbances *nor* impaired renal function (intermediate risk)
- LDH > 2 x ULN *and* bulky disease; LDH > 2 x ULN *and* renal impairment *and/or* electrolyte disturbance: high risk.

Patients may receive pre-phase treatment for approximately 3 days, and if necessary, the investigator may extend pre-phase treatment with prednisone for a maximum of 7 days.

Pre-phase Medication	Dose	Duration
Prednisone	100 mg/d	Recommended day-3 to day -1

9.2. Induction treatment

9.2.1. Treatment schedule in induction therapy

During the induction therapy phase, patients will receive a maximum of six 21-day cycles of loncastuximab tesirine and nine 28-day cycles of epcoritamab. The administration of loncastuximab tesirine will be intravenously (iv) at a dose of 150 µg/kg on day 1 for the first 2 cycles, followed by 75 µg/kg on day 1 of each subsequent 21-day cycle in responding patients for a maximum of 4 cycles subsequently (6 cycles in total). To prevent tumor lysis syndrome, loncastuximab tesirine should be administered 7 days prior to the initiation of epcoritamab.

Epcoritamab will be administered subcutaneously (sc) using a step-up dosing regimen. The priming dose will be 0.16 mg sc on day 1 of cycle 1, followed by 0.8 mg sc on day 8, and full doses of 48 mg on cycle 1 day 15 and day 22. In cycles 2-3, epcoritamab will be administered once every week (QW), followed by once every 2 weeks (Q2W) in cycles 4 to 9, and once every 4 weeks (Q4W) in cycles 10 to 13, as detailed in the study flow chart (Section 1.5).

For both agents the doses approved according to Summary of Product Characteristics (SmPC) are not allowed to be exceeded (i.e. 150 µg/kg for loncastuximab tesirine and 48 mg for epcoritamab).

Table 2. Treatment regimen for loncastuximab tesirine and epcoritamab during induction therapy:

Treatment regimen loncastuximab tesirine, cycle 1-2 (21 day cycle): loncastuximab tesirine iv 150 µg/kg Day 1 **Treatment regimen loncastuximab tesirine, cycle 3-6 (21 day cycle):** loncastuximab tesirine iv 75 µg/kg Day 1 **Treatment regimen epcoritamab, cycle 1 (28 day cycle), start 7 days after loncastuximab tesirine:** epcoritamab sc 0.16 mg Day 1; 0.8 mg Day 8; 48 mg Day 15 and 22 **Treatment regimen epcoritamab cycle 2-3 (28 day cycle):** epcoritamab sc 48 mg Day 1,8,15,22 **Treatment regimen epcoritamab cycle 4-9 (28 day cycle):** epcoritamab sc 48 mg Day 1,15

For details concerning the treatment administration refer to Tables 2-3 as well as 8.3, 8.4 (premedication), 9.4.1 and 9.4.2 (study drugs administration) and to 9.5 (dose adjustments).

9.3. Consolidation therapy

Consolidation will comprise monotherapy with epcoritamab at a dose of 48 mg by subcutaneous injection every 4 weeks from cycle 10 to cycles 13 or until disease progression or relapse, , death, major protocol deviation, pregnancy, patient or investigator decision whichever occurs first. Only patients who achieve at least partial response at the end of the induction phase are eligible for the consolidation phase with epcoritamab.

Table 3. Treatment regimen epcoritamab during consolidation therapy:

Treatment regimen for epcoritamab beyond cycle 9 (4 weeks cycle, cycles 10-13): epcoritamab SC 48 mg Day 1

9.4. Study drug administration

9.4.1. Loncastuximab tesirine

Loncastuximab tesirine will be administered as an iv infusion over 30 minutes on Day 1 of each cycle, which occurs every 3 weeks. The initial dose will be 150 µg/kg every 3 weeks for 2 cycles, followed by a maintenance dose of 75 µg/kg every 3 weeks. Please refer to Section 8.3 for information on premedication and Section 8.5 for supportive care guidelines.

9.4.2. Epcoritamab

Epcoritamab will be administered via sc injection. Please refer to Section 8.4 for information on premedication and supportive care. The preferable injection sites are the lower part of the

abdomen or the thigh. It is recommended to alternate the injection site between the left and right side, especially during weekly administration.

Premedication with corticosteroids, antihistamines, and antipyretics is mandatory for the first four doses of epcoritamab, as described in Section 8.4. An additional 3 days of corticosteroids are required following each of these first 4 doses to prevent or reduce the severity of symptoms related to potential CRS. The premedication should be given at least 30 minutes before administering epcoritamab.

On days when corticosteroid is given to manage epcoritamab side effects and overlaps with a day of corticosteroid administration for loncastuximab tesirine, the dose of corticosteroid prescribed for managing epcoritamab toxicity should be administered prior to loncastuximab tesirine but not later than 120 minutes before the subsequent epcoritamab dose (refer to Sections 8.3 and 8.4). If this does not apply, an additional 4 mg of dexamethasone should be given 30 minutes prior to epcoritamab administration.

For the first 4 doses of epcoritamab, the subject or medical stuff in case of inpatient treatment must perform oral temperature monitoring three times a day (approximately every 6-8 hours during waking hours) for the first 4 days after epcoritamab administration using the thermometer. These temperature checks are to monitor for the development of fever, which is an early sign of CRS (refer to Appendix D).

Premedication with corticosteroids can be administered either iv or orally (PO) at the recommended dose or equivalent (refer to Sections 8.3 and 8.4). The subject should be monitored according to local SOC, which may include blood draws, vital sign changes, and neurological assessments, to detect any signs of ICANS events.

During the first 4 epcoritamab administrations, the following measures should be considered unless medically contraindicated:

- Increase oral fluid intake during the 24 hours prior to each epcoritamab administration.
- Hold antihypertensive medications for 24 hours prior to each epcoritamab administration.
- Administer a small volume (e.g., 500 mL) of isotonic intravenous fluids prior to each epcoritamab administration on the same day.
- Increase oral fluid intake during the 24 hours following each epcoritamab administration.

Patients should be hospitalized for at least 24 hours after receiving the Cycle 1 Day 15 dosage of 48 mg.

9.5. Dose adjustments

It is recognized that attributing causality of any adverse event to the test drugs may be difficult. However, in Phase I and II studies, certain adverse events were observed exclusively in relation to loncastuximab tesirine and/or epcoritamab. Based on this knowledge, the investigator may decide on necessary dose modifications. Dose modifications and treatment interruptions for loncastuximab tesirine and epcoritamab must be documented and carried out according to the guidelines provided below. The investigator may deem a more conservative dose modification to be appropriate. If these guidelines are not followed, the rationale for other measures must be documented in detail in the patient's medical record. Deviations from the guidelines must be discussed with the sponsor. The use of myeloid growth factors in the therapeutic setting is permitted during study treatment at the investigator's discretion.

For AEs related to both loncastuximab tesirine and epcoritamab, the administration of both drugs (loncastuximab tesirine + epcoritamab) should be delayed. If epcoritamab dosing is held according to the guidelines below, either due to an AE unrelated to loncastuximab tesirine or the initiation of an epcoritamab re-priming cycle, loncastuximab tesirine should be continued if tolerated and deemed appropriate by the investigator and as per the guidelines below. If loncastuximab tesirine is held according to the guidelines below, then epcoritamab may be continued with the following provisions:

- If deemed appropriate by the investigator.
- If the subject is not experiencing CRS, ICANS/neurotoxicity (except for grade ≤ 2 peripheral neuropathies present at baseline), CTLS, and/or other epcoritamab-related AEs that would necessitate withholding epcoritamab.

If the above provisions are met, then at the investigator's discretion, epcoritamab may be continued weekly during cycles 2-3, every 2 weeks during cycles 4-9, or once every 4 weeks starting from cycle 10 to cycle 13.

The following requirements must be fulfilled before initiating a new dose of loncastuximab tesirine at the beginning of each cycle:

Table 4. Criteria to be met before next loncastuximab tesirine:

Neutrophils ≥ 1,000/mm^3 (if not related to bone marrow infiltration)
Platelets ≥ 50,000/mm^3 (if not related to bone marrow infiltration)
No edema, effusion, AST/ALT grade ≤ 2
No other non-hematological adverse events CTC grade 3 or 4

The following requirements must be met before starting a new epcoritamab dose within each cycle:

Table 5. Criteria to be met before next epcoritamab:

Neutrophils ≥ 500/mm^3 (if not related to bone marrow infiltration)
Platelets ≥ 50,000/mm^3 (if not related to bone marrow infiltration)
No CRS and/or MAS/HLH, and/or ICANS
No other non-hematological adverse events CTC grade 3 or 4

For neutropenia grade ≥3 (< 1,000/mm^3) consider administration of G-CSF according to local guidelines.

If the above-mentioned requirements are not fulfilled, delay infusion until the criteria are met.

The following dose levels of **loncastuximab tesirine** should be used for dose reductions:

Table 6. Dose levels of loncastuximab tesirine:

Dose level 0: 150 µg/kg (original dose level cycle 1-2) and 75 µg/kg kg (original dose level cycle 3-6)
Dose level -1 (cycle 2): 75 µg/kg
Dose level -2 (cycle 3-8): 37.5 µg/kg (lowest dose level)
If more dose reduction is required, discontinue loncastuximab tesirine permanently

There are no dose reductions for **epcoritamab**. Re-priming should be used instead of dose reductions at certain time points as described below. A re-priming consists of a weekly schedule of a priming dose, intermediate dose, and 2 full doses:

Table 7. Re-priming of epcoritamab:

Step-up dosing for epcoritamab re-priming:
- 0.16 mg sc re-priming dose on Day 1
- 0.8 mg sc intermediate dose on Day 8
- 48 mg sc first full dose on Day 15
- 48 mg sc second full dose on Day 22

A re-priming cycle should occur for the following:

- If intermediate dose is delayed more than 1 day (i.e., intermediate dose would occur more than 8 days after priming with 0.16 mg): repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.
- If first full dose is delayed more than 7 days (i.e., first full dose is planned to occur more than 14 days after intermediate dose with 0.8 mg): repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.

- After first full dose applied, if the interval between the previous dose of epcoritamab and next planned dose exceeds 6 weeks: repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. Then resume the planned dosage.

Patients should remain hospitalized for a minimum of 24 hours after receiving the re-priming cycle Day 15 dose of 48 mg.

After the completion of re-priming, the subject should continue treatment with the remaining loncastuximab tesirine treatment cycles in a manner that allows for the occasional administration of epcoritamab and loncastuximab tesirine on the same day within the treatment schedule (see flow chat, Section 1.5). It is important to note that all doses of epcoritamab must be given at least 7 days apart.

If dosing is restarted with the priming or intermediate dose, the 4-day consecutive corticosteroid regimen (day of epcoritamab dosing plus 3 days after) must also be repeated for CRS prophylaxis (refer to Section 8.3) until at least 2 full doses are re-administered within the appropriate dosing windows without subsequent occurrence of CRS grade ≥ 2 (see details below on CRS). Hospitalization for a minimum of 24 hours is required for the administration of the first full dose of 48 mg epcoritamab at cycle 1 (Day 15) or subsequent re-priming. Any preplanned hospitalization for monitoring CRS will not be considered a serious adverse event (SAE) unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization occurs.

Patients should perform self-administered temperature monitoring at home for the first 4 days after epcoritamab administration during cycle 1. For cycle 2 and beyond (including any cycles in which re-priming occurs), temperature checks are recommended if CRS occurs following the 4th epcoritamab administration in the previous cycle or as determined by the investigator.

A planned dose of epcoritamab can be postponed for up to 6 weeks at the investigator's discretion. If a dose is delayed for more than 6 weeks, discussion with the sponsor medical monitor is required. If a dose is delayed for over 4 weeks, the subject should be asked to come in for an unscheduled visit to collect information on AEs, concomitant medications, laboratory values (including hematology, biochemistry, and coagulation values), and undergo a limited physical examination. If epcoritamab has to be discontinued, the monotherapy with loncastuximab tesirine (max. 6 cycles) should be continued according to the protocol (refer to Table 2 as well as Sections 9.2.1, and 9.4.1).

9.5.1. Dose modification of loncastuximab tesirine for non-hematologic toxicity

If a patient experiences any grade ≥3 (≥2 for edema and effusion) non-hematologic adverse events including increased AST, ALT and total bilirubin > grade 3 as well as cutaneous

collagenous vasculopathy and capillary leak syndrome, the administration of loncastuximab tesirine has to be paused until the toxicity resolves to grade ≤1.

Refer to Section 9.6.3 for further information on management in the setting of liver function tests abnormalities.

If the dosing of loncastuximab tesirine is delayed by more than 3 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, subsequent doses of loncastuximab tesirine should be reduced by 50%. Additionally, at the investigator's discretion, the dose of loncastuximab tesirine may be reduced by 50% for any grade ≥3 (≥2 for edema and effusion) toxicity that is possibly related to loncastuximab tesirine but does not result in a dosing delay of more than 3 weeks if it is deemed to be in the best interest of the patients. If toxicity requiring dose reduction as described above occurs following the second dose of 150 µg/kg (C2D1), the patient should receive the per protocol-defined dose of 75 µg/kg for cycle 3. If the described toxicity recurs at the reduced dose, subsequent doses of loncastuximab tesirine should be further reduced by an additional 50% (37.5 µg/kg).

If the described toxicity recurs after a lowest dose reduction (37.5 µg/kg), the study drug must be permanently discontinued. If the dosing of loncastuximab tesirine is delayed by more than 5 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, the study drug must be permanently discontinued unless continued administration is approved by the Sponsor. In this case, epcoritamab monotherapy should be continued according to the protocol (refer to Tables 2-3 as well as Sections 9.2.1, 9.3, and 9.4.2).

9.5.2. Dose modification of loncastuximab tesirine for hematologic toxicity

If a patient experiences absolute neutrophil count less than 1,000/mm^3 or platelet count less than 50,000/mm^3, loncastuximab tesirine must be held until neutropenia resolves to grade ≤ 2 (≥1,000/mm^3) and thrombocytopenia to grade ≤ 2 (≥50,000/mm^3). If dosing is delayed by more than three 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, subsequent doses must be reduced by an additional 50%. A maximum of two dose reductions are allowed.

9.6. Special precautions and management of adverse events following administration of loncastuximab tesirine

9.6.1. Edema and pleural effusion

Serious cases of effusion and edema have been reported in patients receiving loncastuximab tesirine, with approximately 5.6% of patients experiencing grade ≥3 edema and effusion. To manage these conditions, standard doses of spironolactone should be administered to patients who exhibit weight gain greater than 1 kg from cycle 1 day 1, new or worsening edema, and/or new or worsening pleural effusion. The dose of spironolactone may be adjusted as clinically

necessary. Additional diuretic support may be considered if there is further increase in weight, edema, or pleural effusion.

Patients should be instructed to monitor their weight on a daily basis, preferably in the morning at around the same time each day. If they observe a weight gain of more than 1 kg from their baseline weight, they should promptly notify the study site. This weight monitoring is important for early detection of potential fluid retention and timely intervention.

Diagnostic imaging should be considered in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnoea, chest pain, and/or ascites such as swelling in the abdomen and bloating

9.6.2. Photosensitivity and cutaneous reactions

Severe cutaneous reactions including photosensitivity reactions, have been reported in previous studies involving loncastuximab tesirine (3.7% grade 3). Patients should be advised to minimise or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Patients should be instructed to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered. In clinical studies with loncastuximab tesirine oral and topical corticosteroids and anti-pruritic therapy were used to treat cutaneous reactions.

9.6.3. Liver function tests abnormalities

In clinical studies, abnormal liver function tests of grade ≥3 were reported in 19.5% of patients, with 17.2% of patients experiencing grade 3 or 4 elevation in gamma-glutamyl transferase (GGT) levels. Grade 3 elevations in ALT and AST were reported in 2.8% and 0.9% of patients, respectively.

Management of hepatic enzyme elevations should be driven by assessment of AST and/or ALT. For Grade 1 AST or ALT elevation, continue study treatment with liver function test monitoring at each scheduled visit. For Grade 2 AST or ALT elevation, study treatment may be continued with increased liver function test monitoring (at least weekly) until values resolve to normal or baseline. For Grade 3 or 4 AST or ALT elevation, withhold loncastuximab tesirine as per Section 9.5.1; monitor LFTs every 24-48 hours until decreasing, then weekly; evaluate for concurrent etiologies (i.e. viral hepatitis, concomitant medications, disease progression) and consider hepatology consultation. Resume study treatment when resolved to Grade ≤1 or baseline.

For nonhematological adverse reactions, if any AE grade 3 or higher occurs, withhold loncastuximab tesirine until the toxicity resolves to grade 1 or less.

9.6.4. Myelosuppression

Treatment with loncastuximab tesirine carries the risk of severe myelosuppression. In previous studies, 24% of patients experienced grade 3 or 4 neutropenia, 15.8% had grade 3 or 4 thrombocytopenia, and 11.6% had grade 3 or 4 anemia. Febrile neutropenia occurred in 3.3% of patients. Regular monitoring of blood counts is therefore crucial. For guidance on the management of hematologic toxicity, please refer to Section 9.5.2 in the provided documentation.

9.7. Special precautions and management of toxicities following administration of epcoritamab

9.7.1. Guidelines for CRS grading and management recommendations

Based on previous data, CRS has been documented in 51% of patients receiving epcoritamab at the recommended dose. Grade 1 CRS occurred in 37% of patients, grade 2 in 17%, and grade 3 in 2.5% of patients. Recurrent CRS occurred in 16% of patients. The majority of CRS events (92%) occurred during cycle 1. The median time to onset of CRS from the most recent administered epcoritamab dose across all doses was 24 hours (range: 0 to 10 days), and the median time to onset after the first full 48 mg dose was 21 hours (range: 0 to 7 days). CRS resolved in 98% of patients, and the median duration of CRS events was 2 days (range: 1 to 27 days).

The identification of CRS is primarily based on clinical presentation. If CRS is suspected, management should be conducted according to the recommendations listed in Table 8 and Appendix D of the provided documentation. Patients experiencing grade 2 or higher CRS (such as hypotension unresponsive to fluids or hypoxia requiring supplemental oxygenation) should be closely monitored with continuous cardiac telemetry and pulse oximetry, following the institution's standard of care. For severe or life-threatening CRS, intensive-care supportive therapy is necessary.

Supportive care for CRS may include, but is not limited to, the following measures:

- Infusion of saline
- Systemic administration of corticosteroids, antihistamines, and antipyretic medications
- Blood pressure support using vasopressin or vasopressors
- Oxygen support with low-flow or high-flow oxygen and positive pressure ventilation for hypoxia
- Administration of monoclonal antibodies targeting interleukin (IL)-6R, IL-6, or IL-1, such as tocilizumab, siltuximab, and/or anakinra, via parenteral administration
- Blood product support, anti-infectives, analgesics, and appropriate skin and mouth care should be provided according to local guidelines and the investigator's discretion.

The dose modification of epcoritamab in case of CRS is presented below:

Table 8. Dose modification of epcoritamab for CRS:

ASTCT grade	Hold Treatment (Y/N)	Epcoritamab Dose Modification/Pre-Medication
Grade 1	Y	After hold and event resolution, epcoritamab dosing may continue at the discretion of the Investigator
Grade 2	Y	Hold epcoritamab until CRS event resolves: if grade 2 or higher CRS occurs with the second full dose or beyond, administer CRS prophylaxis with the next dose until an epcoritamab dose is given without subsequent CRS (of any grade).
Grade 3	Y	First episode: Hold until full resolution of CRS event. Second episode of the same AE considered related to epcoritamab: Hold epcoritamab until CRS event resolves. If grade 2 or higher CRS occurs with the second full dose or beyond, administer CRS prophylaxis with the next dose until an epcoritamab dose is given without subsequent CRS (of any grade)
Grade 4	Y	Permanently discontinue epcoritamab

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; N = no; Y = yes. Refer to Appendix D.

9.7.2. Guidelines for macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) grading and management recommendations

In cases where cytokine release syndrome (CRS) is reported, evaluation for macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) should be considered. There have been reports of CRS associated with findings of MAS/HLH, and the physiology of these syndromes may overlap. HLH/MAS diagnosis should be considered in the presence of unexplained elevated liver function tests or cytopenias, with or without CRS. Clinical evaluation should include assessing the patient's overall status, including the presence of fever and splenomegaly. Laboratory tests that may aid in the diagnosis include, but are not limited to, complete blood count (CBC), triglycerides, fibrinogen, ferritin, and soluble interleukin-2 receptor.

If MAS/HLH is suspected, management should follow the recommendations outlined in Table 9 and Appendix F of the provided documentation.

Table 9. Dose modification of epcoritamab for MAS/HLH:

Diagnosis	Hold Treatment (Y/N)	Epcoritamab Dose Modification/Pre-Medication
Suspected MAS/HLH	Y	Withhold study treatment. Refer to Appendix F for treatment guidelines for suspected MAS/HLH
Confirmed MAS/HLH	Y	Withhold study treatment. Subjects may resume epcoritamab if: • the subject has fully recovered from MAS/HLH • continued treatment is deemed to have a favorable benefit-risk ratio • approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. Refer to Appendix F for treatment guidelines for confirmed MAS/HLH

N = no; Y = yes. Refer to Appendix F.

9.7.3. Recommendations for management of ICANS grading and management

In the dose-expansion cohort of a phase I/II study, 6.4% (10/157) of patients who received epcoritamab at the recommended dose experienced ICANS. Among these cases, grade 1 ICANS was observed in 4.5% of patients, grade 2 ICANS in 1.3% of patients, and there was one fatal event (0.6%). Of the 10 ICANS events, 9 occurred within cycle 1 of epcoritamab treatment. The median time to onset of ICANS was 16.5 days (range: 8 to 141 days) from the start of treatment and 3 days (range: 1 to 13 days) relative to the most recent administration of epcoritamab. The median duration of ICANS was 4 days (range: 0 to 8 days), with ICANS resolving in 90% of patients with supportive care.

Neurotoxicity will be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) grading for ICANS, which involves the use of the immune effector cell-associated encephalopathy (ICE) assessment tool[52]. All other neurological toxicities (or non-ICANS events) will be graded based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria.

If ICANS is suspected, management should adhere to the recommendations provided in Table 10 and Appendix E of the provided documentation. These guidelines outline the appropriate steps to be taken in the management of ICANS, ensuring the best possible care for patients.

Table 10. Dose modification of epcoritamab for ICANS:

ASTCT Grade	Hold Treatment (Y/N)	Epcoritamab Dose Modification/Pre-Medication
Grade 1	Y	Epcoritamab interruption until resolution of event. Resume epcoritamab at the discretion of the Investigator.
Grade 2	Y	Epcoritamab interruption until full resolution of event. Second episode of event considered related to epcoritamab: Consult Sponsor Medical Monitor to discuss how to proceed.
Grade 3	Y	First episode: Epcoritamab interruption until full resolution of event. Second episode: Permanently discontinue epcoritamab at the discretion of the investigator, if clinically indicated.
Grade 4	Y	Permanently discontinue epcoritamab

ASTCT = American Society for Transplantation and Cellular Therapy; N = no; Y = yes. Refer to Appendix E.

9.7.4. Myelosuppression

Among patients who received the recommended dosage of epcoritamab in dose-expansion cohort of a phase I/II clinical trial, grade 3 or 4 decreased neutrophils occurred in 32%, decreased hemoglobin in 12%, and decreased platelets in 12% of patients. Based on the severity of cytopenias, temporarily withhold or permanently discontinue epcoritamab (see Table 5) should occur. The prophylactic granulocyte colony-stimulating factor administration should be considered.

9.7.5. Infections

Epcoritamab can cause serious and fatal infections. In the dose-expansion cohort of a phase I/II clinical trial, serious infections, including opportunistic infections, were reported in 15% of patients treated with epcoritamab at the recommended dose with grade 3 or 4 infections in 14% and fatal infections in 1.3%. The most common grade 3 or greater infections were sepsis,

COVID-19, urinary tract infection, pneumonia, and upper respiratory tract infection. Patients should be monitored for signs and symptoms of infection prior to and during treatment with epcoritamab and be treated appropriately. The administration of epcoritamab should be avoided in patients with active infections. The prophylaxis of pneumocystis jiroveci pneumonia (PJP) and herpes virus infection should be provided prior to initiating treatment with epcoritamab. Immunoglobulin levels will be measured regularly within the course of study (see Section 1.6). Immunoglobulin replacement therapy (IgRT) is recommended for patients with IgG level < 4 g/l and recurrent infections or a severe infection.

9.7.6. Guidelines for prophylaxis and treatment of tumor lysis syndrome

Subjects who are considered to have an increased risk for clinical tumor lysis syndrome (CTLS) e.g., due to the type of lymphoma, tumor burden (bulky disease and/or elevated lactate dehydrogenase [LDH]), renal impairment, and/or elevated uric acid) should be considered for hydration and prophylactic treatment with a uric acid-lowering agent, as well as frequent monitoring according to local standards or available guidelines[53].

Close monitoring of laboratory parameters to allow for early diagnosis of possible CTLS is recommended.

In cases of CTLS, the epcoritamab dose should be withheld until the tumor lysis syndrome has resolved. Please refer to Appendix G for details regarding the classification and management of tumor lysis syndrome.

9.7.7. Epcoritamab dose modification of other epcoritamab-related AEs

For all other all other epcoritamab-related AEs refer to the table below:

Table 11. Dose modification of epcoritamab of all other epcoritamab-related AEs:

CTCAE Grade	Hold Treatment (Y/N)	Epcoritamab Dose Modification
Grade 1	N	Continue epcoritamab at the discretion of the Investigator
Grade 2	N	Continue epcoritamab at the discretion of the Investigator
Grade 3	Y	First episode: Hold treatment until improvement to grade ≤ 2 or resolution to baseline. Second episode of the same AE considered related to epcoritamab: Hold treatment until improvement to grade ≤ 1 or resolution to baseline at the discretion of

		the Investigator. Permanently discontinue if no improvement in grade within 14 days.
Grade 4	Y	Permanently discontinue epcoritamab at the discretion of the investigator, if clinically indicated.

9.8. Definition of dose-limiting toxicities

Dose-limiting toxicity (DLT) will be defined as any of the following events (see below) occurring from start of cycle 1 of loncastuximab tesirine until 21 days after cycle 2 and from start of cycle 1 of epcoritamab until 7 days after cycle 1 observed in the safety run-in phase at a given dose level, and deemed by the investigator and/or the sponsor to be possibly, probably, or definitely related to loncastuximab tesirine and epcoritamab. Toxicities/adverse events will be assessed using NCI-CTCAE Version 5.0. In case of persistent disagreement between the sponsor and investigator assessments, the opinion of the Data and Safety Monitoring Committee (DSMC) will be decisive.

General:

- Delay of > 3 weeks of cycle 3 of loncastuximab tesirine and/or > 2 weeks of cycle 2 of epcoritamab due to study treatment-related toxicity

Non-hematologic DLT:

- Any non-hematologic toxicity grade ≥ 3:

Hematologic DLT:

- Febrile neutropenia at any grade
- Any sustained haematological toxicity grade 4 or higher
- Grade 3 platelet count decreased (platelet count 25,000/mm^3 to > 50,000/mm^3) with serious bleeding
- Signs of serious bleeding and/or international normalized ratio (INR) increased or partial thromboplastin time (PTT) prolonged as grade 3 (> 2.5 ULN)

For certain toxicities, such as laboratory assessments without a clear clinical correlate (e.g., lipase increase without signs of clinical pancreatitis), a discussion between the investigator and the sponsor may occur to determine if that adverse event should be classified as a DLT necessitating dose reduction.

9.9. Treatment discontinuation criteria

A patient should discontinue treatment with loncastuximab tesirine and/or epcoritamab if any of the following events occur. If it is unclear which drug caused the toxicity, both agents should be discontinued. The reason for discontinuation and the date of discontinuation must be documented for all patients. Patients who discontinue treatment will be not discontinued from the study. Please note that once a patient is discontinued from the study for any reason, re-enrollment is not permitted.

9.9.1. Discontinuation from study treatment

A patient may stop study treatment for any of the following reasons:

- Disease progression
- Unacceptable toxicity:
  - Grade 4 non-hematologic toxicity, as determined by the investigator's judgment.
  - Recurrence of grade 3 non-hematologic toxicity at re-challenge, as determined by the investigator's judgment, despite adequate preventive measures, regardless of timing (e.g., within the same cycle or at a subsequent cycle)
  - Grade ≥2 non-hematologic toxicity that does not resolve to grade ≤1 or baseline, despite delaying treatment for at least 5 weeks after the preceding administration of loncastuximab tesirine and/or at least 6 weeks after the preceding administration of epcoritamab.
- Participant´s decision
- Participant`s non-compliance
- Major protocol deviation
- The Investigator determines that it is in the best interest of the patient to discontinue study treatment
- Discontinuation of the study by the Sponsor
- Pregnancy
- Death

Discontinuation of study drugs does not automatically indicate withdrawal from the study. Patients who discontinue the study drug will be asked to undergo an End-of-Treatment (EOT) visit (Section 11.4) and continue with the Follow-up period (Section 11.5) as outlined in the protocol. The investigational site should make every effort to complete follow-up according to the protocol. If patients are unable to return to the site, site staff may obtain patient status,

including but not limited to survival status, via phone or mail. If induction therapy is discontinued due to toxicity or any other reason, except for toxicity, patients will be discontinued from study treatment and proceed directly to the follow-up phase without consolidation therapy.

9.10. Compliance

Upon termination of the study or at the request of the sponsor or its designee, the pharmacist must return the study drug to the sponsor or its designee, following the proper accounting of all drug supplies. Alternatively, if agreed upon by both the sponsor and the site, the study drug may be destroyed at the site. Instructions regarding the accountability for the study drug are provided in the Site Investigational Product Procedures Manual.

Therapy will be administered as an iv infusion and sc injection by qualified study-site personnel. The details of each administration, including the date, start and stop time of the infusions/injections, dose, and volume infused/injected, will be recorded in the eCRF. The site pharmacist will maintain a log of all study drug preparations for infusion/injection and administration. Drug supplies for each subject will be inventoried and accounted for throughout the study. The infusion/injection will be administered in accordance with approved institutional guidelines.

10. INVESTIGATIONAL MEDICINAL PRODUCT(S) (IMP)

10.1. Investigational Medicinal Product 1: Loncastuximab tesirine 10 mg/vial

The safety information in this protocol is based on the Investigator's Brochure (IB) in its latest version.

10.1.1 Therapeutic indications

Loncastuximab tesirine (ADCT-402) has been investigated for the treatment of B-cell hematologic malignancies. In the United States, loncastuximab tesirine has been approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL NOS, DLBCL arising from low-grade lymphoma, and HGBL. Loncastuximab tesirine received licensure from the U.S. FDA on April 23, 2021. In the European Union, the EMA granted conditional approval for the treatment of adult patients with r/r DLBCL and HGBL after two or more lines of systemic therapy on December 20, 2022.

10.1.2. Physical description

Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate (ADC) composed of a humanized monoclonal antibody (RB4v1.2) targeting the CD19 antigen which is expressed specifically on B-lymphocytes, except plasma cells. The antibody is conjugated through a

cathepsin-cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin. The attached toxin, SG3199, is also known as tesirine[54]. CD19 is highly expressed on the majority of B-cell malignancies, such as B-cell lymphoma (88% of cases) and B-cell leukemia (100% of cases)[55], making it an attractive target for ADC therapy. The CD19 antigen is rapidly internalized by the cell[56, 57], facilitating effective targeting with an ADC therapy.

Upon binding to CD19-expressing cancer cells, loncastuximab tesirine delivers the PBD dimer cytotoxin into the cells. PBDs are naturally occurring anti-tumor antibiotics found in Streptomyces. The PBD monomers bind to the DNA minor groove and form a covalent aminal linkage to the exocyclic N2 amino group of guanine within purine-guanine-purine sequences. PBD dimers, formed by joining two PBD monomers via a polymethylene tether, can create highly cytotoxic DNA interstrand cross-links, preventing the separation of opposing strands and inducing lethal DNA lesions[58].

10.1.3. Storage and handling

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

10.1.4. Preparation, dosage and administration information of loncastuximab tesirine

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 is reconstituted with 2.2 mL of sterile water for injection, resulting in a final volume of 2.0 mL at a concentration of 5 mg/mL. The reconstituted solution is gently swirled to ensure complete dissolution and homogeneity and visually inspected. Study sites are responsible for providing sterile water for injection. Detailed instructions for the reconstitution of the lyophilisate and further dilution of the reconstituted solution can be found in the Pharmacy Instructions. Loncastuximab tesirine is administered intravenously over 30 minutes in a normal intravenous solution. The initial dose is 150 µg/kg iv for 2 cycles, followed by 75 µg/kg iv on day 1 of each 21-day cycle in responding patients for subsequent 4 cycles (6 cycles in total). For reducing a lymphoma burden and decresing the risk of TLS, loncastuximab tesirine will be initiated intravenously 7 days prior to the initiation of epcoritamab.

10.1.5. Overdose

Since loncastuximab tesirine is administered intravenously under the supervision of a healthcare professional, the likelihood of accidental overdose is very low. There is currently no available data to determine the effects of an overdose with loncastuximab tesirine or whether it can be reversed. In the event of an overdose, there is no specific treatment for loncastuximab

tesirine overdose. Symptomatic treatment and standard supportive care measures should be applied to manage any observed toxicity.

10.1.6. Manufacturing, labeling and supply

Loncastuximab tesirine will be supplied as a lyophilized formulation in a clear glass vial by Sobi Pharma AG. Each vial contains a total of 10 mg of loncastuximab tesirine. The vials will be appropriately labeled and distributed to the study sites by the Pharmacy Department of the University Hospital Münster (Universitätsklinikum Münster), specifically the Stabsstelle Apotheke (Pharmacy Department).

10.1.7. Accountability, return and destruction

Loncastuximab tesirine vials should be stored at a temperature of 2°C to 8°C, within the original outer package, in a secure location. Primary and secondary packaging must be stored together. At the study site, the receipt of loncastuximab tesirine will be documented, including the date of receipt, amount, batch number, and expiry date. For each infusion administered to a patient, the drug accountability form will record the subject identification code, date of reconstitution, date of infusion, amount, batch number, and expiry date. The remaining study medication will be destroyed after the completion of the study, in compliance with applicable regulations. The destruction process will be documented. Prior written approval from the sponsor is required for the site to either return all unused study medication or destroy it on-site, in accordance with applicable regulations. Unauthorized destruction of unused study medication without the sponsor's prior written approval is not permitted.

10.2. Investigational Medicinal Product 2: Epcoritamab 4 mg/0.8 ml vial and 48 mg/0.8 ml vial

The safety information in this protocol is based on the IB in their latest version.

10.2.1. Therapeutic indications

Epcoritamab is currently being investigated for the treatment of B-cell lymphomas as a monotherapy and in combination with cytostatic agents or biologicals[20, 29, 30, 31]. Based on its response rate and durability of response, epcoritamab received accelerated approval from the FDA on May 19, 2023, making it the first bispecific antibody approved for the treatment of adults with r/r DLBCL NOS including DLBCL arising from indolent lymphoma, and HGBL, after two or more lines of systemic therapy[59]. On 20 July 2023, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for epcoritamab for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy[60]. Subsequently, the EMA granted conditional approval for the treatment of adult patients with r/r DLBCL and HGBL after two or

more lines of systemic therapy on September 22, 2023. Meanwhile, epcoritamab has been approved as a monotherapy for the treatment of patients with r/r FL after two or more lines of systemic therapy.

10.2.2. Physical description

Epcoritamab (GEN3013) is a bispecific antibody (BsAb) that recognizes both the T-cell antigen CD3 and the B-cell antigen CD20. It is generated through controlled Fab-arm exchange, combining a humanized IgG1λ CD3ε-specific antibody and a human IgG1κ CD20-specific antibody 7D8, each containing complementary mutations (F405L and K409R) necessary for the formation of DuoBody molecules[61, 62]. Epcoritamab has a typical IgG1 structure and biochemical characteristics of a human IgG1 antibody. Additional mutations were introduced in the Fc domain to suppress Fc-mediated effector functions involving human FcγRs or C1q. These mutations prevent non-specific T-cell activation through FcγR-dependent CD3 crosslinking, ensuring that T-cell activation strictly depends on simultaneous binding to CD3 and CD20[34]. Epcoritamab is being developed as a therapeutic agent for the treatment of B-cell malignancies expressing CD20[34, 35]. Epcoritamab exhibits apparent affinity values in the low nanomolar range for binding to CD3 and CD20.

The mechanism of action of epcoritamab involves inducing T-cell activation and subsequent T-cell-mediated cytotoxicity by simultaneously binding to CD20 on target cells and CD3 on T-cells.

Epcoritamab has been shown to induce target-specific activation, proliferation, and cytotoxic activity of both CD4+ and CD8+ T-cells. This effect was observed with various CD20-expressing B-cell lymphoma cell lines, peripheral blood B-cells, patient-derived B-NHL tumor cells, and B-cells from chronic lymphocytic leukemia (CLL) patients. Combination studies of epcoritamab with standard-of-care agents for B-cell NHL demonstrated no antagonism in terms of T-cell activation and T-cell-mediated cytotoxicity. Nonclinical studies using humanized mouse models of B-cell lymphoma xenografts showed potent *in vivo* anti-tumor activity for epcoritamab. In cynomolgus monkeys, epcoritamab induced profound and reversible depletion of peripheral blood and lymphoid organ B-cells at all dose levels. For more detailed information, please refer to the IB.

10.2.3. Storage and handling

Epcoritamab vials should be stored in a secured location protected from light within the original outer package at a temperature of 2°C to 8°C. For further instruction on dilution and handling of diluted solution, please refer to Pharmacy instructions.

10.2.4. Preparation, dosage and administration information of epcoritamab

Epcoritamab is provided as a concentrate for solution in glass vials as 4 mg/0.8 mL and 48 mg/0.8 mL single-dose vials. The solution is sterile, clear to slightly opalescent, and can range from colorless to slightly yellow. It should be free of any visible particles. Detailed instructions for dilution and dose preparation for different epcoritamab doses (0.16 mg, 0.8 mg, and 48 mg) can be found in the Pharmacy Instructions. During administration, the required volume of epcoritamab should be injected into the subcutaneous tissue of the lower part of the abdomen, which is the preferred injection site, or the thigh. It is recommended to alternate the injection site between the left and right side, especially during the weekly administrations in cycles 1 to 3. It is important to avoid injecting epcoritamab into areas with tattoos, scars, or skin that is red, bruised, tender, hard, or not intact.

10.2.5. Overdose

The therapeutic dose of epcoritamab is 48 mg. An overdose is defined as a patient receiving a dose of epcoritamab exceeding 10% of the specified dose in the protocol. Up to the data cut-off date of January 31, 2022, one accidental overdose of epcoritamab occurred due to the pharmacy using the wrong vial with a concentration of 60 mg/mL instead of 5 mg/mL. As a result, the subject received 960 µg of epcoritamab instead of the intended 80 µg, constituting an overdose. This accidental overdose was not associated with any serious adverse events (SAEs). If a higher dose of epcoritamab is administered than intended, the subject should be closely monitored, and appropriate symptomatic and supportive care should be initiated based on the best medical practice guidelines.

10.2.6. Manufacturing and labeling

Epcoritamab will be provided as a concentrate for solution in glass vials. The available vial sizes are 4 mg/0.8 mL and 48 mg/0.8 mL, both in single-dose vials. The manufacturer of Epcoritamab is AbbVie. Epcoritamab will be labeled according to the requirements of local law and legislation. A system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose can be traced back to the respective bulk batch. The labeling of Epcoritamab will be handled by AbbVie and distribution of Epcoritamab to the study sites will be handled by the Universitätsklinikum Münster, specifically the Stabsstelle Apotheke (Pharmacy Department) of the University Hospital Münster.

10.2.7. Supply, accountability, return and destruction

At the study site, the receipt of epcoritamab, including the date of receipt, amount, batch number, and expiry date, will be carefully documented. For each injection administered to a patient, the subject identification code, date of reconstitution, date of injection, amount, batch

number, and expiry date will be recorded on the drug accountability form. After the completion of the study, any remaining study medication will be disposed of in accordance with applicable regulations. The destruction process will be conducted following the appropriate guidelines, and all relevant details will be documented. If approved in writing by the sponsor, the site may choose to either return all unused study medication to the sponsor or destroy it on-site in compliance with the relevant regulations. It is important to note that the destruction of unused study medication without prior written approval from the sponsor is strictly prohibited.

11. STUDY CONDUCT AND STUDY ASSESSMENTS

Diagnostics including follow-up diagnostics follow routine procedures. There are no mandatory trial-specific methods concerning diagnostics and data sampling. Individual procedures given in the protocol represent recommendations, which may be modified by the investigator.
The procedures will be conducted as outlined in the following sections and in accordance with the schedule in Section 1.5 and 1.6.

11.1 Screening visit

A patient must provide written consent before undergoing any protocol-required assessments. Clinical examination and laboratory tests must be performed within 2 weeks, imaging techniques and lumbar puncture within 4 weeks (if necessary) and bone marrow biopsy within 8 weeks prior to the initiation of study therapy. If an examination was conducted prior to obtaining consent, the respective result can be used to determine the subject's eligibility provided it is a standard procedure.

Patients will undergo the following screening procedures (Day -28 to Day -1) to verify study eligibility:

- Patient's history including assessment of constitutional symptoms (B-symptoms): assessment for the presence of drenching night sweats, unintentional weight loss of > 10% of body mass in the previous 6 months and/or fever > 38°C without identifiable cause
- Determination of height and weight
- Clinical examination including vital signs (blood pressure, heart rate, temperature, etc.)
- Neurological assessment
- Determination of ECOG performance status before pre-phase treatment (see Appendix A)
- Histological confirmation of the diagnosis relapsed/refractory aggressive B-cell lymphoma (DLBCL, HGBL or FL grade 3B) based on an excisional biopsy of a lymph node, an appropriate sample of a lymph node, or a biopsy not older than 3 months.

- Electrocardiogram
- Echocardiogram
- SARS-CoV-2 rapid antigen test for SARS-CoV-2 infection (only if a subject has signs/symptoms suggestive of SARS-CoV-2 to rule out infection)
- Laboratory tests (see Section 1.6):

  - Blood count with differential blood cell count
  - Chemistry panel with sodium, potassium, LDH, calcium, magnesium, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase, creatinine, calculation of GFR by CDK-EPI, BUN, glucose, total protein, albumin, lipase, Beta2-microglobulin
  - Thyroid function test: TSH (free T3 and free T4, if abnormal TSH result)
  - Coagulation panel PT/INR, PTT
  - Lipid panel
  - Urine analysis
  - HIV serology, CMV PCR, CMV IgM and IgG, hepatitis B and hepatitis C serology (patients with positive HBV serology should consult with a liver disease specialist before starting of treatment and they should be monitored and managed according to local medical standards of care to prevent HBV reactivation)
  - Tuberculosis (TB) screening by interferon gamma release assay (IGRA) if clinically indicated (e.g., clinical signs and symptoms of TB, contact history, or if the subject lives in or has traveled to or lived in the WHO high TB burden countries)
  - Immunoglobulins (IgA, IgG, IgM)
  - Urine or serum beta-hCG pregnancy test in women of childbearing potential (see Section 8.7)
  - Testing for G6PD deficiency only in cases when G6PD deficiency is suspected

- FDG-PET: the procedure is compulsory and highly recommended to be performed as FDG-PET/[full-dose] CT procedure with FDG-PET and diagnostic CT acquisition as a single procedure, alternatively FDG-PET/MRI is allowed
- CT/MRI or equivalent, informative imaging techniques of involved regions outside of neck/thorax/abdomen (if clinically indicated)
- Bone marrow diagnostics (cytology, flow cytometry, and histology) not older than 8 weeks (no indication if FDG-PET at screening is non-suspicious for bone marrow involvement)

- Only for patients with clinical suspicion of CNS involvement:

- MRI scan of brain

- Lumbar puncture with CSF cytology and flow cytometry

11.2 Treatment period

If after screening a patient is eligible for study participation, patients will receive a maximum of 6 therapy cycles of loncastuximab tesirine, each lasting 21 days, and a maximum of 5 cycles of epcoritamab, each lasting 28 days. Subsequently, monotherapy with epcoritamab will be continued every 28 days for up to one year from the initiation of epcoritamab (a maximum of 13 cycles) or until disease progression or relapse, unacceptable toxicity, death, major protocol deviation, pregnancy, patient or investigator decision whichever occurs first.

The following procedures will be performed at least once per cycle of loncastuximab tesirine and/or epcoritamab:

Prior to each therapy cycle with loncastuximab tesirine:

- Patient's history including assessment of constitutional symptoms (B-symptoms)
- Clinical examination including vital signs (blood pressure, heart rate, temperature, etc.), weight and edema
- Determination of ECOG performance status (see Appendix A)
- Electrocardiogram
- Laboratory tests (see Section 1.6):

- Blood count with differential blood cell count

- Chemistry panel with sodium, potassium, LDH, calcium, magnesium, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase, creatinine, calculation of GFR by CKD-EPI, BUN, glucose, total protein, albumin, lipase

- Coagulation panel PT/INR, PTT
- Thyroid function test: TSH (free T3 and free T4, if abnormal TSH result)

- Urine or serum beta-hCG pregnancy test in women of childbearing potential (see Section 8.7)
- Urine analysis

- Whole blood ctDNA (MRD)[d] (C1D1 pre-dose only)

- Immuno-phenotyping (exploratory) (C1D1 pre-dose only)[d]

- T-Cells, B-Cells, NK cells (TBNK) by flow cytometry pre-dose (C1D1 only)

Prior to application of epcoritamab dose:

- Patient's history[a] including assessment of constitutional symptoms (B-symptoms)
- Clinical examination including vital signs (blood pressure, heart rate, temperature, etc.) before and 1 hour (+30 minutes) post-epcoritamab administration
- Determination of ECOG performance status (see Appendix A)[a]
- Electrocardiogram if clinically indicated
- Neurological assessment (ICANS)[b] and ICE score (see Appendix E)
- CRS prophylaxis and temperature monitoring[c]
- Laboratory tests (see Section 1.6):

- Blood count with differential blood cell count[a]
- Chemistry panel with sodium, potassium, LDH, calcium, magnesium, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase, creatinine, calculation of GFR by CKD-EPI BUN, glucose, total protein, albumin, lipase[a]
- Urine or serum beta-hCG pregnancy test in women of childbearing potential on Day 1 of epcoritamab after EOT with loncastuximab tesirine (see Section 8.7)
- Clinical tumor lysis syndrome (CTLS) to be monitored on Day 1 of epcoritamab and subsequently as clinically indicated in subjects while receiving study drug therapy. Refer to Appendix G.
- CMV-PCR (every third epcoritamab cycle: D1C3, D1C6, D1C9, D1C12)
- Quantitative monitoring of IgM, IgA, IgG (every third epcoritamab cycle: D1C3, D1C6, D1C9, D1C12)
- Urine or serum beta-hCG pregnancy test in women of childbearing potential on day 1 of each epcoritamab cycle as soon as not controlled anymore prior to loncastuximab tesirine due to end of treatment or loncastuximab tesirine discontinuation (see Section 8.7)
- Whole blood ctDNA (MRD)[d] pre dose (only on C2D1, C3D1, C6D1, C13D1 EOT, or in case of relapse/progression, or subject discontinuation, whichever comes first)
- Immuno-phenotyping (exploratory) pre-dose (C1D1, C2D1, C3D15, C5D1, EOT, or in case of relapse/progression, or subject discontinuation, whichever comes first)[d]
- T-Cells, B-Cells, NK cells (TBNK) by flow cytometry pre-dose (only on C1D1, C2D1, C3D1, C6D1, C9D1, C13D1 of epcoritamab)[d]

Twice per week:

- Laboratory tests: Blood count with differential blood cell count

Throughout therapy cycles:

- Assessment and documentation of AEs and SAEs (see Section 13.5 and 13.6)
- Electrocardiogram (if clinically indicated)

a. If given on day separate from the day of loncastuximab tesirine infusion

b. Further details for ICANS assessments are provided in the Protocol Appendix E.

c. CRS prophylaxis consists of dexamethasone 15 mg daily (or 100 mg prednisone iv or oral) for cycle 1 or re-priming cycle (Days 1 to 4, 8 to 11, 15 to 18, 22 to 25). Subject should perform oral temperature monitoring 3 times a day (approximately every 6 - 8 hours during waking hours) for the first 4 days post-epcoritamab administration. Details in Section 8.4 and Section 9.4.2.

d. Refer to Section 1.6 and Appendix H for details on biomarker sample collection, respectively.

11.3 Interim restaging

There is repeated staging (response assessment) every 6 weeks for 6 months after starting treatment, then every 3 months within the next 6 months until end of treatment or as clinically indicated. The following procedures will be performed at any interim restaging:

- Patient's history including assessment of constitutional symptoms (B-symptoms)
- Clinical examination including vital signs (blood pressure, heart rate, temperature, etc.)
- Determination of ECOG performance status (see Appendix A)
- Electrocardiogram
- Laboratory tests (see Section 1.6)
  - Blood count with differential blood cell count
  - Chemistry panel with sodium, potassium, LDH, calcium, magnesium, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase, creatinine, calculation of GFR by CDK-EPI, BUN, glucose, total protein, albumin, lipase
  - Urine or serum beta-hCG Pregnancy test in women of childbearing potential (see Section 8.7)
  - Thyroid function test: TSH (free T3 and free T4, if abnormal TSH result)

- FDG-PET based imaging for restaging is highly recommended. If PET-CT or PET-MRI cannot be performed, contrast-enhanced CT scans of neck, thorax and abdomen are to be performed. Assessment und documentation of AEs and SAEs (see Section 13.5 and 13.6)

11.4 Final restaging/end of treatment visit (EOT)

Approximately 4-6 weeks after the last cycle of study drugs, whichever is administered last, the procedures listed below will be performed during the final restaging.

- Patient's history
- Clinical examination including vital signs (blood pressure, heart rate, temperature, etc.)
- Determination of ECOG performance status (see Appendix A)
- Electrocardiogram
- Laboratory tests (see Section 1.6):
  - Blood count with differential blood cell count
  - Chemistry panel with sodium, potassium, LDH, calcium, magnesium, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase, creatinine, BUN, calculation of GFR by CDK-EPI, glucose, total protein, albumin, lipase
  - Thyroid function test: TSH (free T3 and free T4, if abnormal TSH result)
  - Coagulation panel PT/INR, PTT
  - Urine or serum beta-hCG Pregnancy test in women of childbearing potential (see Section 8.7)
  - CMV-PCR
  - Urine analysis
  - Whole blood ctDNA (MRD)[d]
- FDG-PET: the procedure is highly recommended to be performed as FDG-PET/full-dose-CT procedure with FDG-PET and diagnostic CT acquisition as a single procedure. PET-MRI is also allowed.
- If no FDG-PET is performed: contrast-enhanced CT scan of the neck/thorax/abdomen (MRI of neck/thorax/abdomen also accepted)
- CT/MRI or equivalent, informative imaging techniques of involved regions outside of neck/thorax/abdomen (if clinically indicated)

- Bone marrow diagnostics (cytology and histology; only when bone marrow was initially involved)

11.5 Follow-up examinations

A first follow-up should be performed 6 weeks after the end of therapy with study drugs. Thereafter, 3-monthly follow-up examinations are recommended during the first 2 years after the completion of therapy, followed by 6-monthly follow-up visits. Follow-up observation within the study will end for all patients 3 years after the last patient was enrolled in the study.

The follow-up examinations should include the following procedures:

- Patient's history
- Clinical examination including vital signs (blood pressure, heart rate, temperature, etc.)
- Determination of ECOG performance status (see Appendix A)
- Electrocardiogram
- Laboratory tests (see Section 1.6):
  - Blood counts with differential blood cell count,
  - Chemistry panel with sodium, potassium, LDH, calcium, magnesium, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase, creatinine, BUN, calculation of GFR by CDK-EPI, glucose, total protein, albumin, lipase
  - Thyroid function test: TSH (free T3 and free T4, if abnormal TSH result)
  - Coagulation panel
- CT scan of the neck/thorax/abdomen (neck/thorax/abdomen: MRI also accepted, neck: ultrasound also accepted). All CT scans performed during the follow-up period later than 6 months after the last restaging are optional. Thus, CT scans should be performed at the first and second follow-up examination.
- To exclude a secondary neoplasm, diagnosis of progressive disease or relapse histological confirmation by biopsy of the respective lesion should be pursued.
- Assessment und documentation of AEs and SAEs. The documentation ends 150 days after the last application of loncastuximab tesirine and/or epcoritamab (whichever is applied last) (please refer to Section 13.5 and 13.6)

11.6 Restaging in case of early discontinuation of therapy

In cases of early discontinuation of therapy (see Section 9.9.1), a restaging examination should be conducted as soon as possible to determine the success of treatment at the time of

discontinuation: procedures should include the same as those for the final restaging on completion of therapy (see Section 11.4).

11.7 Staging in case of progression or relapse after study therapy

In case of progression or relapse after study therapy, FDG-PET scans (preferably) or CT scans or other adequate imaging methods need to be performed to identify the sites of lymphoma involvement.

11.7.1 Laboratory analysis

Laboratory assessments are conducted by local laboratory facilities or external laboratories. The investigator must verify the qualification of these facilities to perform the required analyses. It is the investigator's discretion to determine whether laboratory values are noteworthy or fall outside the expected range. Abnormal values should not be considered an adverse event (AE) unless they are associated with a clinically relevant condition (Section 13.1)

11.7.2 Pathological analysis

The primary histological diagnosis will be determined by a local pathologist based on the examination of a biopsy obtained from a completely excised lymph node or an appropriate extranodal tumor sample. The report provided by the local pathologist must include the histological diagnosis. The primary histological diagnosis is required during the screening process.

11.7.2.1 Reference pathology

Reference pathology will be conducted following procedures established by the GLA study group and by the German Panel of reference pathologists in the Competence Network on Malignant Lymphomas.

The biopsy leading to the diagnosis of relapsed/refractory lymphoma (DLBCL, HGBL, FL grade 3B) must be sent for the reference pathology within 14 days of the patient's inclusion in the study. The necessary documents and the working instruction titled 'Reference Pathology' will be included in the ISF. For simplicity, Italian centers are required to refer to Prof. A. Rosenwald (Würzburg), who will act as a coordinating pathologist. German center should refer to one of the reference pathologists in the Competence Network on Malignant Lymphomas presented below:

Prof. Dr. med. F. Fend	Institut für Pathologie, Universitätsklinikum Tübingen Liebermeisterstraße 8 72076 Tübingen Tel.: (+49) 07071 29-80207

	Fax: (+49) 07071 29-2258
Prof. Dr. med. M.-L. Hansmann	Institut für Pathologie und Molekularpathologie Helios Universitätsklinikum Wuppertal Heusnerstraße 40 42283 Wuppertal Tel: (+49)0202 896 2486
Prof. Dr. med. W. Klapper	Institut für Pathologie, Lymphknotenregister der Universität Kiel Michaelisstraße 11 24105 Kiel Tel.: (+49) 0431 500-15716 Fax: (+49) 0431 500-15714
Prof. Dr. med. G. Ott	Abteilung für Klinische Pathologie, Robert-Bosch-Krankenhaus Stuttgart Auerbachstraße 110 70376 Stuttgart Tel.: (+49) 0711 8101-3390 Fax: (+49) 0711 8101-3619
Prof. Dr. med. A. Rosenwald	Institut für Pathologie, Universität Würzburg Josef-Schneider-Str. 2 97080 Würzburg Tel.: (+49) 0931 31-81247 Fax: (+49) 0931 201-47440

Also will be acting as reference pathologist for this study:

Prof. Dr. med. S. Hartmann	Senckenbergisches Institut für Pathologie, Universitätsklinikum Frankfurt Theodor-Stern-Kai 7 60590 Frankfurt am Main Tel.: (+49) 0696 30-15364 Fax: (+49) 0696 30-13903

11.7.3 Imaging techniques

To ensure consistent and high diagnostic quality of imaging, FDG-PET, MRI, and CT scans will be conducted in accordance with commonly accepted recommendations for quality control in multicenter trials. Additionally, mandatory quality control is performed for all FDG-PET, MRI, and CT scanners as required by legal regulations.

11.7.4 Evaluation of therapy effect

The evaluation of therapy effectiveness will be based on the results of interim and final restaging, and assessed by investigator, following the response criteria defined below. The remission criteria have been established based on the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification, and have been appropriately modified for application within a large-scale multicenter trial for aggressive lymphoma (refer to Appendix C).

Note: In accordance with the "Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification," a partial response (PR) does not imply the necessity of additional therapy. PR will continue to be defined as such as long as a residual mass is detectable by CT, except for FDG-PET-negative residual masses which are designated as complete response (CR). FDG-PET-positive sites at the time of final restaging should not trigger any therapy, unless active disease is confirmed by a biopsy of the FDG-PET-positive site. In the latter case, we recommend consulting the Central Study Office.

The appearance of new PET-avid lesions while all other previous lesions have disappeared, decreased in measurable size, or in FDG-avidity, will be considered progressive disease (PD). Measurable extralymphatic disease should be assessed in a manner similar to nodal disease. The spleen and Waldeyer's ring are considered lymphatic tissue. Disease manifestations that can be assessed but not quantitatively measured (e.g., pleural effusions) will be recorded as present or absent unless, while an abnormality is still noted by imaging studies or clinical examination, it is found to be histologically negative for lymphoma involvement.

In cases where diffuse organ infiltration or bone involvement cannot be measured by PET-CT, additional biopsies of the specific site might be necessary. If there is uncertainty regarding the definition of response to therapy, we recommend consulting the Central Study Office."

12 STUDY DURATION, PREMATURE TERMINATION OF THE STUDY

12.1 Expected duration of the trial

Planned start date of the study (FPFV, first patient first visit):	Q4/2025
Planned end of recruitment (LPFV, last patient first visit):	Q2/2027
Planned end of the study:	Q2/2030
Planned duration of individual patient participation:	3-4.5 years*
Planned duration of recruitment:	1.5 years
Planned overall duration of the study:	4.5 years
Planned duration of follow-up:	app. 3 years

*The duration of study varies for each patient because a patient remains in the follow-up until the end of the study.

12.2 Definition of the study end

The study will end 3 years after the last patient enrolled in the study.

12.3 Early study termination for an individual patient

A patient has the right to withdraw their consent and discontinue participation in the study at any time, without any negative impact on their further treatment according to standard clinical practice. Additionally, the investigator may choose to withdraw a patient from study treatment at any time in the interest of patient safety, such as in cases of disease progression or unacceptable toxicity.

12.4 Early termination of treatment

Please refer to Section 9.9.1.

The reason for early termination of the treatment must be documented and the coordinating investigator or his delegate must be informed in writing e.g. on the respective eCRF. Patients who stop therapy early must be documented and followed-up according to protocol.

12.5 Violation of eligibility criteria

Patients who do not meet the eligibility criteria during screening are not eligible to participate in the study. If it is discovered at a later date that a patient was ineligible at the time of inclusion, it does not automatically require early withdrawal from the study. However, the violation must be reported to the Central Study Office and, if applicable, to the responsible investigator. The coordinating investigator will discuss with the investigator whether further treatment within this study is justified or if another treatment is indicated. Documentation of the patient's clinical data will continue, and the patient will be included in the intention-to-treat analysis. The recruitment process will not be affected, and the patient will not be substituted by another patient.

12.6 Early closing of a trial site

Closing a trial site will be considered if:

- It does not meet the technical requirements of the protocol
- The recruitment rate is not sufficient
- The conduct of the study is not compliant with the protocol
- The data quality is insufficient

The decision to close a site early will be made by the sponsor or their delegate. Investigators and trial sites that choose not to participate in the trial any longer must inform the sponsor. The

decision should be well-founded, providing clear reasons for discontinuation. Details regarding further treatment and follow-up of patients already enrolled in the study should be discussed with the sponsor.

12.7 Early termination of the study

Early termination of the study **may be necessary** for the following reasons:

- Occurrence of serious unexpected side effects of treatment
- Excessive treatment-related mortality
- Relevant new information from other studies or publications
- Inadequate recruitment
- Excessive number of deviations from the study protocol
- Logistic and/or financial reasons
- Any other fact which would change the risk-benefit analysis of this trial
- For CAR-T naive patients treated second line: BORR < 60% after second assessment of 20 treated patients by FDG-PET/CT (-MRI)
- Inadequate efficiency irrespective of CAR-T pretreatment status: ORR ≤ 60% after interim assessment of 50 treated patients irrespective of CAR-T pretreated status

The Data Safety Monitoring Committee will regularly monitor the conduct of the study, with particular focus on the safety aspects of the trial. This monitoring will involve reviewing the annual safety report (ASR or DSUR), the results of planned and unplanned safety analyses, and may include providing recommendations to the sponsor regarding trial continuation or protocol changes. The sponsor will then make decisions on the necessary actions after consulting the Protocol Committee. These recommendations will consider factors such as recruitment progress, characteristics of the study population, adherence to the protocol, execution of therapy as per the protocol, and the frequency of adverse events and serious adverse events. The decision to terminate a study early is a complex process that takes into account statistical, medical, ethical, organizational, and financial aspects. The sponsor ultimately bears the final responsibility for early termination of the study. Additionally, in accordance with EU regulation 536/2014 and local laws, the competent authority may suspend or prematurely terminate the trial by its decision. Immediate notification of the early termination of the trial will be provided to all competent authorities and the responsible ethics committee.

12.8 Early termination of follow-up

Every instance of early termination of the follow-up period must be documented by the responsible investigator or their delegate. If feasible, the date, circumstances, and reasons for the termination should be thoroughly documented and communicated to the Central Study Office.

13 ADVERSE EVENTS

13.1 Definition adverse event

‘Adverse event’ means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal clinically significant laboratory finding), symptom, or disease temporarily associated with the use of a (investigational) medicinal product, whether or not considered related to the (investigational) medicinal product. As such, any new sign, symptom, disease, or clinically significant increase in the intensity of an existing sign, symptom, or disease should be considered an AE. This includes any significant worsening observed during interim or final clinical examinations, electrocardiograms, X-rays, and any other safety assessments, irrespective of whether these procedures are required by the protocol.

A pathological finding that improves or remain unchanged compared to its status before signature of the informed consent does not qualify as an adverse event.

Pregnancy, medication errors (e.g., overdose), and uses outside the scope defined in the protocol should always be considered adverse events, even if there are no adverse medical consequences.

Abnormalities in laboratory test values will be reported in the electronic case report form (eCRF). Blood counts will be continuously evaluated during the trial and documented in the respective eCRF. Abnormal values should not be reported on the AE page of the eCRF unless they are associated with a clinically relevant condition. The following laboratory abnormalities should be documented on the AE page:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy
- Hematological toxicity CTCAE grades 3-5 (not grades 1-2)

Clinically significant worsening of the disease under study that occurs during the study is considered an AE. Lack of efficacy of the study drug is not considered an AE unless it leads to other unfavorable medical occurrences.

Adverse events can be reported spontaneously or elicited during open-ended questioning, examination, or evaluation of a subject.

Adverse events should be classified according to the NCI CTCAE V5.0 or ASTCT Consensus Grading, respectively (see 13.4.1). A non-serious adverse event is an AE that is not classified as serious.

13.2 Definition serious adverse event

A “Serious Adverse Event” (SAE) is any untoward medical occurrence that at any dose:

- Results in death (adverse event is the event which led to death, including disease progression)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization (this does not include hospitalizations planned before inclusion in the study, or other hospitalizations without underlying adverse event, e.g. for social reasons)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

SAEs include all serious events independent of whether they have a suspected causal relationship to the investigational medicinal product (IMP) or not.

In addition, other conditions should also be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization

- Potential drug induced liver injury (DILI) is considered an important medical event
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is considered an important medical event
- Any second malignancy is also considered an important medical event
- Although pregnancy, medication errors (e.g. overdose) and uses outside what is foreseen in the protocol are not always serious by regulatory definition, the investigator must handle these events like SAEs
- Product complaints of loncastuximab tesirine or epcoritamab (e.g. quality defect of the product or its packaging, labeling, or medical device component) have to be handled like SAEs, too, even if not associated with an adverse event

NOTE: Cases of disease progression are a result of the underlying disease and primary endpoint of this study. Therefore, these events will not be reported as SAE, as long as they do not result in death. Any death caused by disease progression has to be reported as SAE.

13.3 Pregnancy

If it is discovered after initiating the study treatment that a study subject is pregnant or may have been pregnant during or within 12 months after the study treatment exposure, the administration of the treatment will be permanently discontinued in an appropriate manner, ensuring subject safety (e.g., dose tapering if necessary).

The investigator must immediately notify the sponsor's Safety Desk of this event through the Pregnancy Reporting Form, following the procedures for reporting serious adverse events (SAEs).

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcomes, and if applicable, offspring information, must also be reported on the Pregnancy Reporting Form when available. IMPORTANT: Collecting data on pregnancy outcomes is only permissible if both parents have provided their written consent beforehand.

Any pregnancy occurring in the female partner of a male study participant should also be reported to the sponsor's Safety Desk using the Pregnancy Reporting Form. IMPORTANT: Collecting data on the female partner of a male study participant is only permissible if she has provided her written consent beforehand.

13.4 Classification of adverse events/serious adverse events

13.4.1 Severity

Assessment of severity will be done according to NCI-CTCAE V5.0. CTCAE is available in the investigator site file. The assessment of the severity of CRS and ICANS will be performed according to the Consensus Grading of Adults American Society for Transplantation and Cellular Therapy (ASTCT) (see Appendix E).

13.4.2 Causal relationship of the adverse event/serious adverse event

The investigator must judge whether or not, in his opinion, the adverse event was related with the administration of the investigational medicinal product. SAE reports must also assess causal relationship for each other drug mentioned on the report. The relationship has to be determined by the investigator:

- Reasonable possibility or
- No reasonable possibility.

These values are defined as follows:

- Reasonable possibility: there are facts or arguments to suggest a causal relationship
- No reasonable possibility: time relationship is improbable, and/or another explanation is more likely (e.g. disease or other drugs provide plausible explanation)

Each Serious Adverse Event as defined in Section 13.2 has to be reported, even if the investigator feels that it is not related to the administration of any drug composing the study treatment.

13.4.3 Outcome

The outcome of SAEs has to be classified as follows:

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

13.5 Period of observation, documentation and assessment of AE

The documentation of AEs, including SAEs, begins after signing informed consent form and continues within 6 half-lives (equivalent to at least 150 days) after the last administration of loncastuximab tesirine and/or epcoritamab (whichever is administered last). In the case of early termination of study therapy for an individual patient, documentation of AEs ends either 150 days after the last administration of loncastuximab tesirine and/or epcoritamab (whichever is administered last) or at the start of a new treatment.

If the investigator becomes aware of an SAE that occurs after the end of the reporting period and believes there is a reasonable causal relationship to the study therapy or a protocol-specified procedure, they must, without undue delay, report that late SAE to the sponsor's Safety Desk. Such events occurring before end of trial participation of the patient, have to be documented on the adverse event pages in the eCRF, too.

All AEs, including SAEs, must be recorded in the source document and on the adverse event pages in the eCRF, regardless of whether or not the AE is considered related to the use of study drug(s).

The severity grade of adverse events, classified in accordance with the CTCAE criteria or ASTCT Consensus Grading (see 13.4.1), should be documented in the designated fields in the eCRF. If side effects occur that are not explicitly listed in the eCRF, the relevant adverse event and its severity grade should be classified according to CTCAE v5.0 and recorded.

Non-serious AEs should be followed until resolution or stabilization, and if they become serious, they must be reported as SAEs. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of the study drug, as well as for those that are present at the end of the study treatment as appropriate. All SAEs should be followed to resolution or stabilization.

13.5.1 Adverse events of special safety interest (AESI)

An adverse event of special interest (AESI) is an adverse event (serious or non-serious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by protocol amendment. Based on data from clinical studies with loncastuximab tesirine and epcoritamab, whenever there is a reasonable suspicion of the following AEs, the investigator should immediately notify the Safety Desk within 24 hours. This notification should be done regardless of whether the event is assessed as causally related or not related to the study drug, or as serious or non-serious. The AESI should be recorded on a SAE form, and if the event is assessed as non-serious, the non-serious assessment should be indicated on the form.

The following AE are considered as AE of special interest:

- Edema and effusion ≥ grade 2
- Cutaneous reactions including photosensitivity ≥ grade 3
- AST, ALT, GGT, total bilirubin or alkaline phosphatase ≥ grade 3 or any grade event that led to dose modification (loncastuximab tesirine)
- Cytokine release syndrome (CRS) ≥ grade 3
- Macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH)
- Immune effector cell-associated neurotoxicity syndrome (ICANS) ≥ grade 3
- Infections ≥ grade 3 according to CTCAE
- Tumor lysis syndrome (TLS) ≥ grade 3
- Cutaneous collagenous vasculopathy, any grade (loncastuximab tesirine)
- Capillary leak syndrome, any grade

13.5.2 Pregnancies

The investigator is required to report any occurrence of pregnancy in a female study patient during her participation in this study. The outcome of the pregnancy should be carefully monitored and any information regarding the outcome of both the mother and the child at delivery should be reported.

In the case of a pregnancy in the partner of a male study patient, all possible efforts will be made to obtain comparable information on the course and outcome of the pregnancy, subject to obtaining consent from the partner.
These pregnancy-related reports should be submitted within the same timelines as SAEs.

13.6 Reporting of SAEs by the investigator

The local investigator or their delegate is responsible for reporting any SAE, as defined in Section 13.2, including death, irrespective of the reason, within 24 hours of knowledge. SAEs and AESIs have to be reported to the sponsor's Safety Desk using the SAE form, via fax at +49 (0) 251-83-57-112 or via email to mssd@ukmuenster.de, as long as protection of data privacy is met. This reporting requirement applies regardless of the severity (CTCAE grade or ASTCT Consensus Grading) or whether or not the SAE is considered related to the study drug(s). Before forwarding any information, personal data have to be replaced with the subject identification code.

The following SAEs are exempted from immediate reporting:

- Cases of disease progression, as long as they do not result in death.

Safety Desk Contact	
Address	University Münster Zentrum für Klinische Studien (ZKS) Münster Safety Desk Von-Esmarch-Str. 62 48149 Münster Germany
Phone	+49 (0) 251 83 57109
SAE fax	**+49 (0) 251 83 57112**
Email	**mssd@ukmuenster.de**

SAEs and product complaints should be documented on the SAE Form, while pregnancies should be reported using the Pregnancy Reporting Form. Fax number and email address for submission are provided on each page of the forms. Reporting language is English.
The forms should be completed with as much information as possible, and the investigator should not wait for full details before making the initial report.
The minimum information to be included in any initial SAE report is:

1. Subject identification code
2. SAE details
3. Details about administration of investigational medicinal product/s
4. Causality assessment of SAE to investigational medicinal product/s

5. Reporting investigator

The investigator must promptly inform the sponsor's Safety Desk about any relevant follow-up information regarding reported SAEs on the SAE form. In the case of a death, a copy of an autopsy protocol should be provided if available.

The investigator is responsible for responding to any queries sent by the Safety Desk as soon as possible. It is a legal obligation for the investigator to report SAE information to the sponsor.

The Safety Desk will acknowledge receipt of initial reports within one business day. In case a trial site does not receive an acknowledgement of receipt of an initial report within one business day, it should contact the Safety Desk for clarification.

In the event of a fatal outcome, the investigator also has to supply the competent authority and the Ethics Committee with any details, if requested by them.

SAEs have to be reported from the time at which the informed consent is obtained until 150 days after the last application of loncastuximab tesirine and/or epcoritamab (whichever is administered last), or the start of a new treatment. This is regardless of whether or not they are considered to be drug related.

If the investigator becomes aware of an SAE that occurs after the end of the reporting period and believes there is a reasonable causal relationship to the study therapy or a protocol-specified procedure, they must, without undue delay, report that late SAE to the sponsor's Safety Desk.

Fatal adverse reactions will be considered unexpected as long as the investigational medicinal product is not marketed and these reactions are not listed as possibly fatal in the Reference Safety Information.

13.6.1 SAE reporting requirements by the sponsor

The Sponsor is responsible for all of the pharmacovigilance obligations and safety reporting pursuant to the applicable laws and regulations in the country/countries where the Study is performed.

Additionally, the sponsor shall report certain cases to AbbVie and Sobi. The following reporting obligations as per contractual agreement will be covered by the Safety Desk.

Reports shall be sent to the Sobi Drug Safety department by e-mail (adverseevent@sobi.com), or by fax (+46 8 697 32 30), within 7 calendar days of first awareness if the event is fatal or life-threatening and within 15 calendar days of first awareness for other serious adverse events. The requirement to report includes information on any exposure during pregnancy via the mother or a male partner, or via breastfeeding. The sponsor and investigator shall assist Sobi in obtaining follow-up information for any reported serious adverse event. On an annual basis or at the end of the study (as applicable), the sponsor's Safety Desk shall assist Sobi in

reconciliation between the sponsor's pharmacovigilance database and the Sobi Drug safety database including reconciliation of listings of all serious adverse events and exposure during pregnancy or via breastfeeding in subjects assigned to receive loncastuximab tesirine and epcoritamab. The reporting of serious adverse events, pregnancies and breastfeeding to Sobi does not relieve the sponsor from other regulatory reporting responsibilities.

All other drug safety related correspondence should be sent to drugsafety@sobi.com.

AbbVie's contact for reporting Serious Adverse Events, pregnancies, pregnancy experiences, Safety Signals and Special Situations shall be PPDINDPharmacovigilance@abbvie.com. Serious adverse events shall be sent within 7 calendar days if reporting a death or life-threatening event, and within 15 calendar days for all other SAEs, pregnancies experienced by a trial participant or a partner of a participant or a negative outcome or untoward event during the course of such a pregnancy or upon delivery, safety signals (any event in the study that potentially signals a new causal association with epcoritamab or a new aspect of a known association with epcoritamab) and special situations (pregnancy exposure, overdose, abuse, misuse, medication error, or occupational exposure with epcoritamab), within 15 calendar days.

13.7 Assessment of SAEs by the sponsor

The Safety Desk will document each SAE, check it and query additionally required information. The Coordinating Investigator (or a named delegate) will review each SAE again for seriousness and relatedness. The Coordinating Investigator (or delegate) will also assess whether an SAR is expected or unexpected (SUSAR) according to the applicable Reference Safety Information in the respective reference document (Summary of Product Characteristics or IB, as applicable and submitted to the Competent Authority) and whether any SAE might influence the benefit-risk-ratio or might require changes in the conduct of the trial.

In this context, the following definitions apply:

13.7.1 Definition serious adverse reaction (SAR)

An Adverse Reaction is a response to a medicinal product which is noxious and unintended. The definition also covers medication errors and uses outside what is foreseen in the protocol. All SAEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as SAR. The expression reasonable causal relationship means that there is evidence or argument to suggest a causal relationship.

13.7.2 Definition unexpected serious adverse reaction

An unexpected serious adverse reaction means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the respective reference safety information within the reference document for that product, as submitted to the competent authority.
In determining whether an adverse event is unexpected, consideration shall be given to whether the event adds significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction.

- The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.
- An expected adverse reaction with fatal outcome is considered unexpected as long as the fatal outcome is not explicitly mentioned in the applicable reference safety information. The same applies for an expected adverse reaction, which is life-threatening. It is considered unexpected as long as it is not explicitly mentions as life-threatening in the applicable reference safety information.
- A more specific reaction than labeled is considered unexpected (“acute renal failure” is a labeled AR, a new report of “interstitial nephritis” is more specific and therefore unexpected).
- An increase in the rate of occurrence of an expected adverse reaction, which is judged to be clinically important, is considered as unexpected.

If the reference safety information is contained in an IB, it is located within a clearly-identified section including information on the frequency and nature of adverse reactions. Applicable Reference Safety Information is the version in the respective reference document in effect and approved for the trial at time of occurrence of the serious adverse reaction.

13.7.3 Definition suspected unexpected serious adverse reaction (SUSAR)

Any case fulfilling the criteria of an unexpected serious adverse reaction is a SUSAR.

13.8 Legal reporting requirements of the sponsor

13.8.1 SUSAR Reporting

It is the duty of the sponsor’s Safety Desk to ensure that the Competent Authority (via EudraVigilance) is informed of all SUSARs in accordance with legal requirements (fatal or life threatening SUSAR as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction, completed report, if required, within an additional 8 days; all other SUSARs immediately, not later than 15 days after the sponsor became aware

of the reaction). SUSAR follow-up reports will be submitted, if appropriate. The Safety Desk will inform all investigators concerned about SUSARs at time of submission or by 6-monthly listings including a summary, as deemed appropriate according to the amount and relevance of the SUSAR cases. The responsible Ethics committees may be involved by the Member States.
SUSAR reports will also be supplied to the Data Safety Monitoring Committee (DSMC).

The Safety Desk will observe SUSAR cross reporting obligations with other trials of the same sponsor investigating any of the same active substances.

13.8.2 Other safety issues

The Coordinating Investigator is responsible for the ongoing safety evaluation of the trial. The Sponsor shall notify the Member States concerned of all unexpected events which affect the benefit-risk balance of the clinical trial (besides SUSARs). That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.
Where an unexpected event is likely to seriously affect the benefit-risk balance, the Sponsor and the Investigator shall take appropriate urgent safety measures to protect the subjects. A notification to the Member States concerned shall be made without undue delay but no later than seven days from the date the measures have been taken.

Other safety issues might be, for instance:

- An increase in the rate of occurrence, which is judged to be clinically important
- Any new events related to the conduct of the trial or the development of the investigational medicinal products and likely to affect the safety of the subjects (this might include product complaints)
- A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial
- A significant hazard to the subject population such as lack of efficacy of an investigational medicinal product used for the treatment of a life-threatening disease
- A major safety finding from a newly completed animal study (such as carcinogenicity)
- Any anticipated end or temporally halt of a trial for safety reasons and conducted with the same investigational medicinal products in another country by the same sponsor
- Recommendations of the DSMC, if any, where relevant for the safety of the subjects

13.8.3 Annual safety report

Annual safety reports will be prepared and submitted in accordance with legal requirements (Development Safety Update Report, DSUR).

The Coordinating Investigator is responsible for providing the updated benefit-risk assessment and passages requiring medical assessment. He will also take care that information about recruitment status and demographics are available, as required. The Safety Desk is responsible for preparing the template, adding the other parts of the report, finalizing it and submitting it to the competent authority in line with legal requirements and in due time. The Ethics committee will be involved by the safety assessing Member State.

The annual report will cover only this trial, as the trial uses a complex therapy regimen. Moreover, the sponsor does not have a development program for the investigational medicinal product loncastuximab tesirine and epcoritamab. The report will be prepared annually from the date of the initial Clinical Trial Authorization and submitted within 60 days of data lock point (day before anniversary of initial authorization). This report will also be supplied to the Data Safety Monitoring Committee (DSMC). Additional reports will be prepared on request by the respective authority or the ethics committee.

14 BIOMETRICAL ASPECTS

14.1 Statistical hypotheses and sample size calculation

The primary aim of the trial regarding efficacy is to estimate the Best Overall Response Rate (BORR) defined as the proportion of r/r DLBCL patients with a best overall response (CR plus PR) whenever it occurs to the combination of loncastuximab tesirine and epcoritamab. The BORR will be reported for each subject up to 12-months of treatment, according to the response categories ordered as CR > PR > stable disease (SD) > PD > not evaluable.

Assumptions for sample size calculation:

120 r/r DLBCL patients will be recruited. With assumed dropout rate of 5%, 114 patients will be evaluable at the end. The BORR of loncastuximab tesirine and epcoritamab was 48% and 63.1% for each, respectively, as reported by Caimi et al., 2021; and Thieblemont et al., 2023. By combining epcoritamab and loncastuximab tesirine we expect to improve the BORR to ≥ 75%. With a sample size of 114 evaluable patients a BORR of 75% can be estimated with a 95% confidence interval (CI) (Clopper-Pearson) ranging from 66% to 83%.

The primary endpoint of the CLEAR study is BORR. Studies with CAR-T cells in second line, ZUMA-7 (n=180) and TRANSFORM (n=92), demonstrated ORR of 83% and 87% respectively[8, 9]. Thus, the pooled BORR is 84% (95% CI: 79-88%). A BORR < 60% of the therapeutic CLEAR regime will be considered not acceptable in CAR-T naive patients. If ≤ 11

of 20 patients achieve a CR/PR the BORR will be ≤ 55% (95% CI: 32-77%), thereby excluding the lower limit of the 95% CI observed in ZUMA-7 and TRANSFORM trials (pooled data). In this situation, after consultation with the DSMB the study will be terminated early for CAR-T naive patients.

An interim analysis will be performed after 50 patients have been included irrespective of pretreatment with CAR-T cells. If the BORR at the time of the interim analysis is ≤ 60% (95% CI: 45% to 74%), the upper limit of the CI excludes an BORR of 75% as expected for the combination of loncastuximab tesirine and epcoritamab, and the study will be terminated early. Calculations will be performed using the software program PASS 2022, v22.0.3.

14.2 Registration of patients

All patients who do not meet the exclusion criteria and fulfill all eligibility criteria upon completion of staging examinations can be registered for the trial. Additionally, patients who were initially assumed to be eligible at the time of inclusion in the study but are later found to not meet the eligibility criteria will also be included in the intent-to-treat analysis of the study if they were treated within the study. Not more than 60 patients with previous CAR-T cell therapy will be included to fulfill the criteria that at least 50% of all treated patients within the study need to be CAR-T naive.

14.3 Endpoints of study

14.3.1 Primary endpoints

Please refer to Section 4.1

14.3.2 Secondary endpoints

14.3.2.1 Secondary endpoints for efficacy

Please refer to Section 4.2

14.3.2.2 Secondary endpoints for safety and toxicity

Please refer to Section 4.3

14.3.2.3 Secondary endpoints for protocol adherence

Please refer to Section 4.4

14.3.2.4 Secondary endpoints for outcome according to lymphoma biology

Please refer to Section 4.5

14.4 Statistical methods for study analysis

Further details will be described in statistical analysis plan (SAP). SAP will be prepared before start of analyses and finalized before database lock. Missing values will not be imputed. Outliers will be identified prior to the analyses of the efficacy endpoints and have to be checked by the investigator.

14.4.1 Analysis populations

The Full Analysis Set (FAS) will include all patients treated with at least one dose of study drug. The primary endpoint Best Overall Response Rate (BORR) will be assessed within FAS. The Safety Analysis Set (SAS) will include all patients who received at least one dose of study drug.

14.4.2 Subgroup analysis

Subgroup analyses regarding CAR-T naive patients and patients failing CAR-T cell therapy, lymphoma type (DLBCL, HGBL, FL grade 3B), primary refractory and relapsed disease, as well as gender are planned. Duration of overall response will also be presented according to response (CR/PR). Further details will be described in the statistical analysis plan (SAP).

14.4.3 Planned methods for analysis

14.4.3.1 Primary endpoint

The primary analysis will determine the BORR with 95% confidence interval.

14.4.3.2 Secondary endpoints

The CR rate, PR rate, progression rate, rate of treatment-related deaths and relapse rate will be documented together with the corresponding 95% confidence intervals (Clopper-Pearson). Further secondary endpoints (data on survival time: PFS, OS, duration of complete response, duration of best response) will be analyzed using a Kaplan-Meier curve/cumulative incidence curve. Survival rates will be presented with 95% confidence intervals.

For qualitative endpoints, such as adverse events and serious adverse events frequency tables will be prepared. Quantitative endpoints, such as laboratory parameters, cumulative doses of drugs, duration of therapy, time to complete response and time to best response will be described in tables displaying sample size, range, mean and standard deviation or medians and quartiles. Kaplan-Meier curves will be presented and log-rank tests will be used for subgroup comparisons of survival data. Multivariate Cox regression models will be performed to adjust for prognostic factors. A statistical analysis plan will be prepared before start of efficacy analyses and finalized before database lock.

14.4.3.3 Safety run-in phase for all study patients

A safety run-in phase will be conducted 60 days after 20 patients started treatment, to assess the safety of the combined administration of loncastuximab tesirine and epcoritamab, specifically regarding observed toxicities. A detailed analysis of all AEs, SAEs, and therapy-associated deaths will be performed. All AEs and SAEs from all available cycles up to this time point will be analyzed and submitted to the CTIS as part of a substantial modification for review and decision-making on the continuation of the study.

The Data Safety Monitoring Committee (DSMC) will also review the available toxicity data and make a decision on the safety and tolerability of the recommended doses of loncastuximab tesirine, epcoritamab, and their combination. Once the dose with acceptable safety and tolerability of loncastuximab tesirine and epcoritamab has been defined by the principal investigator and the DSMC, the study will continue at the determined dose levels. If necessary, an amendment will be submitted before including any further patients in the trial. The trial may be terminated based on the recommendation of the DSMC. The final responsibility for terminating the trial rests with the sponsor. The trial will continue while the safety run-in analysis is ongoing.

14.4.3.4 Efficacy run-in phase for CAR-T naive patients

For patients not pretreated with CAR-T cells, an additional and separate efficacy analysis will be performed after the 20th CAR-T naive patient started treatment with loncastuximab tesirine and epcoritamab and had a second response assessment (12 weeks after treatment start) by FDG-PET/CT (-/MRI). The primary endpoint of the CLEAR study is BORR. Studies with CAR-T cells in second line, ZUMA-7 (n=180) and TRANSFORM (n=92), demonstrated an ORR of 83% and 87% respectively[8, 9]. Thus, the pooled ORR is estimated at 84% (95% CI: 79-88%). For this run-in phase a BORR < 60% is considered not acceptable. If ≤ 11/20 patients achieve a CR/PR the BORR will be ≤ 55% (95% CI: 32-77%), no longer including the lower limit of the 95% CI for BORR observed in ZUMA-7 and TRANSFORM trial (pooled data) and the study will be closed for CAR-T naive patients. In any case, the BORR results will be reported to the DSMC, the members of which will meet to evaluate the efficacy of study drugs in the first 20 CAR-T naive patients included. The members of the DSMC will recommend continuation of the study, require modifications, or stop the study after independent review of all available data. The results of the efficacy run-in phase evaluated by the DSMC will be communicated and discussed with the principal investigator, the study committee, and the sponsor of the study. The final recommendation to continue, modify or stop the study lies with the DSMC. These data will be submitted to CTIS as well as part of a substantial modification for review

and decision-making on the continuation of the study. The study sponsor will follow the DSMC's suggestion to continue, modify or stop the study.

14.4.3.5 Efficacy interim and cumulative safety analysis

An interim analysis will be conducted 6 months after the 50th patient has been enrolled in the study. In terms of efficacy, the study will only proceed if the BORR exceeds 60%. If the BORR is 60% or below, the study may be terminated early. With the efficacy analysis a further safety and protocol adherence analysis will be conducted for the 50 patients included. The analysis will involve a detailed description of AEs, SAEs, dosing of loncastuximab tesirine and epcoritamab, duration of therapy, and therapy-associated deaths. The efficacy and safety data will be submitted to the CTIS as part of a substantial modification for review and decision-making on the continuation of the study. The findings of the interim analysis will also be presented to the DSMC. The recommendations provided by the DSMC may lead to an amendment of the study protocol or closure of the study. The trial will continue while the interim and analysis is being performed.

14.4.4 Criteria for early discontinuation of the study due to safety

SAEs and deaths that occur during the study will be continuously monitored by the sponsor and their delegates. There is no formal criterion for early discontinuation specifically related to these endpoints. The safety profile will be formally analyzed on an annual basis, resulting in the production of an annual safety report. The trial may be terminated based on a recommendation from the DSMC following the results of any of the annual safety analyses or safety analyses conducted during the safety run-in phase or during the interim efficacy analysis. The final responsibility for terminating the trial lies with the sponsor.

14.4.5 Final analysis

36 months after start of treatment of the last patient and when all study documentation is available, a final analysis of the trial will be performed.

14.4.6 Biometrical report

A report for each analysis will be prepared by the responsible biometrician. The final analysis results will be presented in a comprehensive statistical report. This report will include a description of the patient population, the treatment feasibility, safety of therapy (with a specific focus on adverse events), adherence to the protocol, cases of early discontinuation, and the results of the efficacy analysis.

15 CONCOMITANT SCIENTIFIC PROGRAM

After obtaining informed consent from patients, a concomitant program of biological and translational research will be carried out in parallel with the study. The purpose of this research is to gain a deeper understanding of the effectiveness of loncastuximab tesirine and epcoritamab in patients with r/r DLBCL. Throughout the study, various research analyses will be conducted using blood samples and tissue biopsies from lymph nodes, extranodal sites, and bone marrow. Participation in the concomitant scientific program is voluntary, and patients who choose not to participate will still be eligible for the study. All study materials and data collected during the research will be stored for a maximum of 10 years. The results of the concomitant scientific projects will be reported separately and will not be included in the final statistical report. These results may be shared at a later time for further scientific investigation and understanding.

15.1. Patient materials to be included in the concomitant scientific program

15.1.1. Blood samples

Blood will be collected at different time points during the course of the study in order to investigate different factors which might be influencing response to the study treatment and identifying specific risk groups within the study population. See Section 15.2.2 and Appendix H below.

15.1.2. Tissue samples

Formalin-fixed paraffin-embedded (FFPE) tissue samples, mainly lymph node samples, which have been used for diagnosis of relapsed/refractory DLBCL will be analyzed. In some cases bone marrow samples or other samples involved will be examined as well.

15.2. Planned research aims and analyses

15.2.1. Gene expression profiling for determination of the molecular subtype

To assess whether the study treatment is particularly effective in patients with a specific molecular subtype ("cell of origin") of DLBCL, the distinction between activated B-cell type (ABC) or germinal-center B-cell type (GCB) DLBCL will be performed for all patients included in the CLEAR study. FFPE tissue samples will be available for analysis.

To reliably allocate patients to a specific molecular subtype, the NanoString technology will be utilized, specifically the Lymph2Cx assay. Unlike conventional gene expression analyses, this assay measures the expression of only 20 genes (see Table 12), which enables accurate determination of the molecular classification. Previous studies have demonstrated high concordance between the classification obtained from conventional gene expression analyses

using fresh tissue and the results obtained from the Lymph2Cx assay[63]. For this assay, RNA isolation from FFPE tissue biopsies will be performed.

Table 12. Genes for molecular classification by Lymph2Cx-Assay:

TNFRSF13B	Genes, with preferentially higher expression in ABC DLBCL
LIMD1	
IRF4	
CREB3L2	
PIM2	
CYB5R2	
RAB7L1	
CCDC50	
R3HDM1	Housekeeping-genes
WDR55	
ISY1	
UBXN4	
TRIM56	
MME	Genes with preferentially higher expression in GCB DLBCL
SERPINA9	
ASB13	
MALM3	
ITPKB	
MYBL1	
S1PR2	

15.2.2. Mutational analysis/whole exome and RNA sequencing

In addition, a mutational analysis of the lymph node tissue will be conducted. Combining information about the DLBCL subtype and the clinical course from the study, the analysis of the mutational profile can provide insights into suboptimal responses to the treatment of relapsed/refractory aggressive B-cell lymphomas and help identify factors contributing to subsequent relapse/progressive disease. For the mutational analysis, whole exome sequencing will be performed. This comprehensive sequencing approach will allow for various analyses, including the determination of molecular subtypes using the LymphGen algorithm. Additionally, RNA sequencing will be conducted to assess the expression levels of genes associated with lymphoma biology or immune status. Correlations will be made between the treatment response and the obtained results.

15.2.3. Immunohistochemistry

For all available tissue samples, immunohistochemistry (IHC) will be conducted to determine the expression of CD10, BCL2, BCL6, and MUM1, allowing for the allocation of samples to either the germinal-center B-cell (GCB) or non-GCB subtype of DLBCL. The results will be

analyzed using established immunohistochemical algorithms that utilize antibodies optimized for staining paraffin-embedded tissues. Several algorithms have been published, with the algorithm developed by Hans et al.[(64)] being the most widely utilized. Immunohistochemistry results will be compared to those obtained from gene expression profiling analysis. Additionally, the results will be correlated with morphological subtyping in collaboration with the reference pathology department at the University of Würzburg, led by Prof. Andreas Rosenwald.

15.2.4. Fluorescence in-situ hybridization (FISH) for *MYC and BCL2*

Translocations involving the *MYC* gene, occurring concurrently with *BCL2* translocations, have been associated with an inferior prognosis. In this study, all patient samples will undergo FISH analysis to detect translocations involving *MYC* and *BCL2*, and these findings will be correlated with treatment response, probability of relapse, and other clinical parameters. The aim is to investigate whether the adverse effects of *MYC* translocations and other abnormalities can be overcome by the combination of loncastuximab tesirine and epcoritamab.

15.2.5. Expression of CD19 and CD20

The expression of CD19 and CD20 will be measured using RNA sequencing, IHC and flow cytometry. Response will be correlated to the expression status. Testing for CD19 and CD20 expression will not be performed before study entry. Determination and correlative analyses will be performed after study completion.

15.2.6. Biomarker research

Biomarker assessments in this study will involve the evaluation of candidate predictive markers that may help predict the treatment outcome. Additionally, the study will monitor minimal residual disease using circulating tumor DNA (ctDNA) throughout the duration of the study. Biomarker assessments will include the evaluation of B- and T-cell counts, T-cell subsets, T-cell activation/exhaustion/metabolic fitness in peripheral blood and tumor samples. The collection of samples for biomarker analysis will follow the specifications outlined in Appendix H and Table 21.

The information obtained from these sample analyses may be utilized to investigate factors influencing treatment response, address scientific questions related to the disease, and contribute to the development of new therapies and diagnostic tests. The results from these exploratory analyses may not be included in the study report and may be performed in a non-Good Laboratory Practice (GLP) laboratory.

All biomarker samples should be appropriately labeled and shipped as detailed in the study-specific laboratory manual. The Sponsor (or researchers collaborating with the Sponsor) will securely store the samples and associated data with measures in place to ensure

confidentiality. The samples may be retained for further research related to loncastuximab tesirine, epcoritamab, or the disease and its related conditions for a maximum of 10 years after study completion, or as required by local regulations.

Specific instructions for the preparation and storage of archived samples will be provided by the central laboratory, Sponsor, or its designated representative. The collection of samples will adhere to the guidelines outlined in Table 21 (refer to Appendix H).

15.2.7. Total metabolic lymphoma volume (TMLV) at baseline and correlation to response

Total metabolic lymphoma volume at baseline will be determined by means of FDG-PET and correlated with the response including PFS and OS.

16. Documentation, Data Management, Archiving

16.1. Patient indentification list

All subject data will be collected and stored in a pseudonymized form. Each trial patient will be identified by a unique subject identification code, which will include a study identifier (e.g., CLEAR) and a three-digit Patient ID. A confidential subject identification list, which links the patients' names with their respective subject identification codes, will be securely stored in the investigator site file.

16.2. Data handling and record keeping

16.2.1. Case report forms

The Case Report Form (CRF) will be designed by the coordinating investigator in collaboration with IMISE/ZKS Leipzig, using an electronic CRF system. The investigator or an authorized member of the study team will access the database via the internet and enter data directly into the database using the eCRF data entry masks. The eCRF should be completed shortly after each study visit.

Each page of the eCRF will be electronically signed by the investigator or an authorized member of the study team. This electronic signature serves as the equivalent of a signature on paper, confirming the accuracy and integrity of the data entered on the eCRF. If any values on the eCRF are later changed, the electronic signature will be automatically reset, and it must be signed again by the principal investigator or an authorized member of the study team. This ensures that changes on the eCRF are properly documented with a date and signature. All entries and data changes will be automatically tracked, including the date, time, and person responsible for entering or changing the information (audit trail). Any major corrections or significant missing data must be explained.

If the Principal Investigator authorizes other members of the study team to enter and sign CRF data, their names, initials, positions, and signatures must be provided to the Sponsor or its authorized representative via the Staff Signature and Delegation Log. However, the investigator retains final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the eCRF.

An eCRF will be assigned to each patient, who will be identified solely by their Patient-ID. All information required by the protocol and collected during the clinical trial must be recorded by the investigator or an authorized member of the study team as source data in the source documentation for the study. Source data, as defined by ICH-GCP E6, include any information in original records and certified copies of original records that contain clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). We expect source data for all items documented on the electronic CRFs.

16.3. Data management

For the creation of the study database, the EDC Tool (secuTrial®) will be utilized. Prior to data capture, the database will undergo validation according to the Standard Operating Procedures (SOPs) of the Clinical Trial Centre Leipzig.

The information entered into the eCRF will be systematically checked for completeness, consistency, and plausibility using predefined rules implemented in the EDC Tool. This allows discrepancies to be addressed during the data entry process. Errors and warnings will be listed in a validation report, and they can be resolved at any time during the entry process. Once data entry is completed, the site staff will flag the eCRF pages as 'data entry completed' (DEC). As part of the on-site monitoring or the central statistical monitoring by the Central Study Office Münster, manual queries may be generated for discrepancies identified after DEC. All eCRF pages with queries will be marked in the system, and a report listing all queries will be available. The site staff will be responsible for data correction and will resolve queries directly in the eCRF pages.

The Central Study Office Münster will supervise and support the resolution of queries and will close all correctly resolved queries. If a query cannot be resolved, the data management staff may close the query in agreement with the study biometrician.

Throughout the study, a daily backup of all data will be performed. Unauthorized access to patient data will be prevented through the access concept of the study database, which is based on a strict hierarchy and role model. Any changes made to the data (e.g., during query management) will be automatically recorded in the database's audit trail.

At the end of the study, once the database has been determined to be complete and accurate, it will be locked.

16.4. Archiving

After the end of the trial, the originals of all trial specific documents (Trial Master File) including originals of the CRFs will be stored by the sponsor in accordance with the applicable regulations (article 58 of EU regulation 536/2014).

16.5. Investigator site file

Each study site keeps an ISF provided by the coordinating investigator. During monitoring, the ISF will be checked regularly for completeness and actuality. After the clinical trial is finished or stopped, the ISF has to be stored by the investigator in accordance with the applicable regulations (article 58 of EU regulation 536/2014).

17. QUALITY CONTROL AND ASSURANCE

17.1 Data safety monitoring committee

A Data Safety Monitoring Committee (DSMC) will be established to provide the sponsor with recommendations regarding study modification, continuation or termination. This includes the decision on how to proceed after the safety analyses of the run-in phase.

The DSMC consists of two clinicians with long-standing experience in the field of lymphoma and one statistician. The DSMC advises and supports the sponsor and the coordinating investigator with regard to patient safety in the course of this clinical trial. For this purpose, the DSMC will evaluate the Development Safety Update Reports (DSUR) and the results of the safety analyses and their influence on the risk-benefit consideration for the patients and the justification of a continuation of study treatment. In addition, the DSMC can evaluate the validity and integrity of the data and, on this basis, the conduct of this trial. Procedures governing the convening and execution of the responsibilities of the DSMC will be specified separately in a written DSMC Charter.

17.2 Monitoring

The trial sites will be monitored to ensure the quality of the collected data. The objectives of the monitoring procedures are to ensure that the trial safety and rights of the trial subjects as a study participant are respected and that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

The investigator agrees that the monitor will visit the study center in appropriate intervals. During these visits the monitor will check the quality of the data recording and ensure that the study center adheres to the study protocol. The investigators agree to provide any relevant information and documentation whenever the monitor requires this information. This includes access to all original study documents and source data.

It is the responsibility of the investigator to keep the participant's chart as complete as possible (e.g. history, concomitant diseases, inclusion in the clinical study, visit dates, results of laboratory tests, distribution of the study medication, and adverse events). Source data are checked and compared with entries in the eCRFs. The participant has given consent with this procedure by signing the patient information and written informed consent form. Additional tasks of the monitor are:

- To check, whether the study center fulfills requirements of the clinical study (e.g. participant population, technical equipment)
- Instruction of the investigators and personnel for the clinical trial
- To check the ISF for completeness and actuality
- Documentation of the status of the participant
- Matching of original data
- To check SAE reports according to regulations

The monitor has the responsibility to treat all information confidentially and to safeguard the integrity and personal privacy of the study participants. The exact extent of the monitoring procedures is described in a separate monitoring manual. The monitoring will be performed with a risk-based approach.

17.3 Audits and inspections

The sponsor may initiate an audit at any study site during the study and after completion. All study-related documentation must be made available to the designated auditor(s).
In addition, representatives of the regulatory authorities may choose to inspect a study center at any time prior to, during, or after completion of the clinical study. In this case, all pertinent study data should be made available as requested to the regulatory authority for verification, or inspection purposes.

18. ETHICAL AND REGULATORY REQUIREMENTS

18.1. Ethical, legal and administrative aspects

The study is conducted in compliance with the declaration of Helsinki (current version, October 2013, Fortaleza). The study is performed in accordance with the requirements of the law of the Member State concerned, the EU Regulation 536/2014, the current legal provisions regarding data protection, and the principles of Good Clinical Practice.
The trial will not start in a participating country until the Member State concerned and the reporting Member State have authorized the clinical trial in accordance with the EU Regulation 536/2014. In order to obtain authorization, the sponsor shall submit an application dossier through the portal referred to in Article 80 of the EU Regulation 536/2014, the Clinical Trials

Information System (CTIS). The application dossier, which includes this study protocol together with all other documents according to Annex I of EU Regulation 536/2014, will be subject to a scientific and ethical review. The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned.

The start of the clinical trial, the first visit of the first subject, the end of recruitment of subjects, the end or early termination of the clinical trial and a temporary halt of the clinical trial shall be notified by the sponsor to each Member State concerned in accordance with articles 36 to 38 of the EU Regulation 536/2014.

Furthermore, the sponsor informs the Member States concerned about a serious breach of the EU Regulation 536/2014 or of the version of the protocol applicable at the time of the breach in accordance with article 52 of the EU Regulation 536/2014.

The sponsor shall also inform the Member States concerned, according to article 53 of the EU Regulation 536/2014, of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not SUSARs. Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects. The sponsor shall notify the Member States concerned of the event and the measures taken (article 54 of the EU Regulation 536/2014).

18.2. Patient information and informed consent

Prior to inclusion into the study, the investigator informs each patient about nature, significance, implications, and risks of the study as well as about the patient's right to withdraw from study participation at any time without any resulting detriment. Further, the patients are informed that insurance has been taken out to cover risks originating from the study. According to the insurance conditions, they are advised to immediately inform the investigator if they were treated for an emergency and not to undergo any other medical treatment without prior consultation with the investigator with the exception of medical emergencies.

Additionally, patients are handed out the patient information including the informed consent form provided for this study. Patient consent in study participation must be given in writing. Before informed consent is requested, patients are left sufficient time for consideration and ask questions in order to clarify any study issues.

According to the General Data Protection Regulation (EU) 2016/679 (GDPR) and national regulations patients are informed that their disease related data are stored in a pseudonymized way and used for scientific evaluations.

The informed consent form is dated and signed by the patient and by the investigator. The originally signed informed consent form is archived in the investigator site file. A copy of the signed informed consent form (or a second original) is handed over to the patient together with a copy of the patient information sheet and a copy of the general conditions of the patient

insurance. If the patient is unable to write, in exceptional cases, instead of the written consent required, oral consent in the presence of at least one witness, who was also included when the patient was being informed may be given. The witness may not be anyone working at the study site nor a member of the investigating team. The orally given consent has to be documented in writing, dated and signed by the witness.

In case of any study issue which requires a change of the patient information sheet, patients already included into the study must, if relevant to them, be informed about these issues orally and in writing and their written consent in further study participation must be obtained.

Note: Before undergoing any study specific procedure the patient must have provided written informed consent!

18.3. Insurance

As required by the EU Regulation 536/2014 and national regulations, patients will be insured against risks originating from the study (subject`s insurance)

In addition, an insurance will be taken covering the risk of accidents patients may have on their way to the study site and back (commuting accident insurance).

A copy of the certificate of insurance and the insurance conditions are provided in the investigator site file. Copies of the insurance conditions are also attached to the informed consent form and have to be handed to the patients.

Insurance company: HDI Global SE, Proactiv-Platz 1, 40721 Hilden.

18.4. Financial support

Sobi and AbbVie will provide the investigational drug loncastuximab tesirine and epcoritamab, respectively. The study will be financially supported by Sobi and AbbVie.

18.5. Adherence to the protocol

The investigator must adhere to the protocol as detailed in this document. Substantial Changes to the protocol will require approval by the concerned Member State and the reporting Member State prior to implementation. This does not apply when the modification is needed to eliminate an immediate hazard(s) to patients.

Any deviations from the protocol must be fully documented in the source documentation and recorded and explained in the CRF (if applicable).

18.6. Protocol amendments

The coordinating Investigator reserves the right to amend the protocol, should this become necessary based on information derived from the study itself or on third-party information which has relevance for the conduct of the trial. Any amendment has to be approved by the Protocol

Committee. After this approval, the amended protocol is sent to the ethics committee(s) and competent authorities in charge. After approval the amendment has to be documented in the Trial Master File with the respective number of the amendment and date when the amendment becomes effective. The amendment becomes effective only after all participants are informed on contents and dates of the amendment.

18.7. Data protection

This study will be performed in compliance with the applicable data protection laws. Study personnel will handle all patient data in a strictly confidential way.

To prevent the identification of a person to whom study data belong, study data will be pseudonymized by means of the patient identification number (see Section 16.1). If patient documents (e.g. examination results) are transferred to an institution outside the study site, copies will be used on which the patient's name and initials or other identifying data are obscured and the patient identification number is indicated.

19. REPORTING AND PUBLICATION POLICY

19.1. Final report

After completion of the biometric evaluation, the coordinating investigator prepares a study report. The report includes all trial results, irrespective of whether favorable or not. It is signed by him and the person who is responsible for the evaluation.

Within 12 months after the end of the study, the sponsor shall submit to the CTIS a summary of the results of the clinical trial. The summary is prepared in the format provided for report synopses by the ICH Guideline E3, "Guidance on Structure and Content of Clinical Study Reports". It shall be accompanied by a summary written in a manner that is understandable to laypersons.

19.2. Safety reports

The rules for the annual safety reports are specified in chapter 13.8.3.

19.3. Publication policy

The results of this study are to be published in the international media. The coordinating Investigator and the Protocol Committee shall decide on authorship taking into account the contribution with respect to study planning, conduct, analysis and the active participation in the study (to be assessed on the basis of numbers of recruited patients). Manuscripts may only be submitted for publication when all authors have approved the contents. The first author will assume that contents of the manuscript have been approved by the co-authors if no requests

for alteration have been received from the co-authors within 2 weeks after receipt of the draft manuscript.

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APPENDICES

APPENDIX A: PERFORMANCE STATUS ACCORDING TO THE ECOG SCALE

General status (ECOG):

Grade 0: Fully functional, no symptoms

Grade 1: Ambulatory patient with symptoms, able to carry out light work

Grade 2: Patient with symptoms, less than 50% of daytime in bed, self-sufficient

Grade 3: Patient with symptoms, more than 50% of daytime in bed, requires some help from others

Grade 4: Completely bedridden and reliant on help from others

APPENDIX B: NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

(The Criteria Committee of the New York Heart Association, Boston: Little, Brown & Co.1994)

NYHA Class	Symptoms
1	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
2	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
4	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

APPENDIX C: STAGING AND RESPONSE ASSESSMENT

Ann Abor staging classification

Stage	Description
Stage I	Involvement of a single lymphatic site (i.e., nodal region, Waldeyer's ring, thymus, or spleen) (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymphatic site (IE)
Stage II	Involvement of two or more lymphatic sites on the same side of the diaphragm (II); or localized involvement of extralymphatic organ(s) or site(s) in association with regional lymphatic site(s) with or without involvement of other lymphatic site(s) on the same side of the diaphragm (IIE)
Stage III	Involvement of two or more lymphatic sites on both sides of the diaphragm (III), or localized involvement of extralymphatic organ(s) or site(s) in association with regional lymphatic site(s) with or without involvement of other lymphatic site(s) on both sides of the diaphragm (IIIE)
Stage IV	Diffuse involvement of one or more extralymphatic organs or sites, with or without associated lymphatic sites; or localized involvement of isolated extralymphatic organ(s) or site(s) in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow.

Stages I to IV should be suffixed A if none of the following symptoms are present and B, if one or more of the following general symptoms are present:
• otherwise unexplained fever > 38°C
• otherwise unexplained drenching night sweats (making change of night clothes necessary)
• otherwise unexplained loss of weight by more than 10% of bodyweight within 6 months

The lymphatic regions used in the Ann Arbor system are as follows:

Region 1:		Waldeyer’s ring including tonsil
Region 2:	right	cervical, supraclavicular, occipital, pre-auricular, nuchal, submandibular
Region 3:	left	cervical, supraclavicular, occipital, pre-auricular, nuchal, submandibular
Region 4:	right	infraclavicular
Region 5:	left	infraclavicular
Region 6:	right	axillary/pectoral
Region 7:	left	axillary/pectoral
Region 8:		mediastinal (including thymus)
Region 9:	right	pulmonary hilus
Region 10:	left	pulmonary hilus
Region 11:		mesenteric
Region 12:		para-aortic (including splenic, hepatic and renal hilus)
Region 13:	right	iliac
Region 14:	left	iliac
Region 15:	right	inguinal/femoral
Region 16:	left	inguinal/femoral
Region 17:		spleen
Region 18:	right	epitrochlear/brachial
Region 19:	left	epitrochlear/brachial
Region 20:	right	popliteal
Region 21:	left	popliteal

Extralymphatic/extranodal (E) involvement

Each of the following count as one extralymphatic/extranodal (E) involvement within the International Prognostic Index (IPI) for DLBCL: bone marrow, lung, liver, skeletal cranial, skeletal caudal, pleura, pericardium, CNS, stomach, small intestine, colon and further E-involvements (see code below). Exception: for skin and soft tissue involvement, each involvement counts. Since the tonsils and the spleen are extranodal but not extralymphatic, they do not count as an E-involvement. Paired organs count as one E-involvement (IPI).

Codes for extralymphatic foci/sites:

Region 22 = Bone Marrow

Region 23 = Lung

Region 24 = Liver

Region 25 = Skeletal, cranial of diaphragm Region 26 = Skeletal, caudal of diaphragm Region 27 = Pleura

Region 28 = Pericardium

Region 29 = Central nervous system Region 30 = Stomach

Region 31 = Small intestine Region 32 = Colon

ORB = orbita

PNS = paranasal sinuses (jaw, forehead, ethmoidal sinus; soft tissue only without skeletal involvement)

MNC = main nasal cavity (soft tissue only without skeletal involvement)

MR = mouth region (oral cavity, lips, pharynx)

TOG = tongue

SG = salivary glands (ear, low jaw salivary glands)

TG = thyroid gland

MG = mammary gland

P = peritoneum

PAN = pancreas

K = kidney

AG = adrenal gland

UB = urinary bladder (including urethra, urinary tract)

TES = testes (including epididymis)

OVA = ovary

UT = uterus

SKN = skin

ST = soft tissues (including muscles, connective tissue and fat tissue)

ASC = ascites
PB = peripheral blood
DIA = diaphragm
OTH = other, please write out

Definition of bulky disease

• massive lymphoma development in a lymph node with the greatest diameter of ≥ 7.5 cm or a conglomerate tumor with a greatest diameter ≥ 7.5 cm
• a mediastinal tumor with a diameter ≥ 7.5 cm, whereby the hili and the pericardium should not be included in the measurement.

The dimensions of bulky disease must be documented in detail in the Staging Report Form. Bulky disease can involve several neighboring regions (conglomerate tumor).

Spleen Involvement

Spleen may be of normal size or enlarged, homogeneous splenomegaly or diffuse infiltration with small lesions or large solid mass.

A single measurement that correlate well with volume is preferable and the cut off > 13 cm in the vertical length for splenomegaly is recommended

Liver Involvement

Measurement of liver size is not reliable by CT and no longer integrated in the Lugano criteria for response assessment.

Bone Marrow Involvement

If applicable, bone marrow involvement uptake in PET is scored using the 5-point scale.

Split lesions and confluent lesions

Lesions may split or may become confluent over time. In the case of split lesions, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression. In the case of confluent lesions, the PPD of the confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The longest (LDi) and smallest diameter (SDi) are no longer needed to determine progression.

International Prognostic Index [65]

The international Prognostic Index (IPI) is an index used to estimate the prognosis of patients with DLBCL. For each of the following risk factors one point is being assigned:

- Age > 60 years
- Ann Arbor stage III or IV
- Elevated serum LDH (> 1 x ULN)
- ECOG performance status ≥ 2
- Extranodal/extralymphatic involvement ≥ 2

Corresponding to the sum of points patients are assigned to one of the following risk groups:

- Low risk 0 or 1 points
- Low-intermediate risk 2 points
- High-intermediate risk 3 points
- High risk 4 or 5 points

Lugano 2014 response classification

Response should be determined on the basis of radiographic and clinical evidence of disease. Assessment of the PET-CT scan should follow the criteria presented below [Cheson et al. 2014].

Response criteria for malignant lymphoma according to Lugano 2014

Table 3. Revised Criteria for Response Assessment

Response and 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†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. 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	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	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	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 (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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 two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. 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 (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†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.

APPENDIX D: GUIDELINES FOR CYTOKINE RELEASE SYNDROME (CRS) GRADING AND MANAGEMENT RECOMMENDATIONS

Table 13. CRS Grading and Recommendations for Management Guidance Based on the American Society for Transplantation and Cellular Therapy Guidelines[a]:

CRS Grade[a]	Supportive Care	Anti-cytokine Therapy[b]	Corticosteroids	follow-up
Grade 1: Fever ≥ 38.0°C, no hypotension, no hypoxia	Hold epcoritamab until resolution of CRS. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Evaluate for other causes of fever and initiate broad spectrum antibiotics per local guidelines to continue until fever resolves; in the case of concurrent febrile neutropenia, follow local guidelines until febrile neutropenia resolves. Supportive care per institutional standard of care (antipyretics and IV hydration) Closely monitor neurologic status	Recommended for patients with advanced age, high tumor burden, circulating tumor cells, rapidly progressing disease, history of major organ dysfunction, elevated inflammatory markers (e.g., CRP, ferritin) or fever refractory to antipyretics. Notes: • If tocilizumab is used, do not exceed more than 2 doses in a 24-hour period • If suspicion of ICANS is concurrent with CRS, choose alternative to tocilizumab	Dexamethasone 10 - 20 mg per day (or equivalent) may be initiated. Note: If suspicion of ICANS is concurrent with CRS, initiation of dexamethasone is highly recommended (see Neurotoxicity guidelines in Appendix E).	Not improving after 24 hours: • Tocilizumab 8 mg/kg iv over 1 hour (not to exceed 800 mg)

CRS Grade[a]	Supportive Care	Anti-cytokine Therapy[b]	Corticosteroids	follow-up
Grade 2: Fever ≥ 38.0°C with hypotension not requiring vasopressors And/or hypoxia requiring low-flow (≤ 6L/min) Oxygen	Hold epcoritamab until resolution of CRS. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Evaluate for other causes of fever and initiate broad spectrum antibiotics per local guidelines to continue until fever resolves; in the case of concurrent febrile neutropenia, follow local guidelines until febrile neutropenia resolves. Continuous cardiac telemetry and pulse oximetry as indicated IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids Supplemental oxygen as indicated	Recommended (refer to notes below) Example: Tocilizumab 8 mg/kg iv over 1 hour (not to exceed 800 mg) Notes: • If tocilizumab is used, do not exceed more than 2 doses in a 24-hour period • If CRS is refractory to 2 doses of tocilizumab, initiate/ increase dose of corticosteroids and consider alternative anti-cytokine therapy. • If suspicion of ICANS is concurrent with CRS, choose alternative to tocilizumab	Recommend dexamethasone 10 - 20 mg per day (or equivalent) Note: If suspicion of ICANS is concurrent with CRS, initiation of dexamethasone is highly recommended (see Neurotoxicity guidelines in Appendix E).	Improving • Discontinue anti-cytokine therapy • Taper corticoste-roids, manage as above Not improving • Manage as grade 3 (below)

CRS Grade[a]	Supportive Care	Anti-cytokine Therapy[b]	Corticosteroids	follow-up

Grade 3:
Symptoms require and respond to aggressive intervention
Fever ≥ 38.0°
with hypotension requiring 1 vasopressor with or without vasopressin[c]
And/or hypoxia requiring high-flow (> 6 L/min) facemask, NC, NRB mask or Venturi mask
	Hold epcoritamab until resolution of CRS.
	In-person evaluation by medical professional, ideally at site or center with experience managing CRS.
	Investigate for infection and rapidly startup broad-spectrum antibiotics.
	Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve.
	Supportive care per institutional guidelines (antipyretics and IV hydration).
	
	In addition:
	• Management in Intensive Care Unit
	• Vasopressor support and/or supplemental oxygen as indicated
	• Consider cardiac echocardiogram
		Recommended (refer to notes)
		Example: Tocilizumab 8 mg/kg iv over 1 hour (not to exceed 800 mg)
		Notes:
		• If tocilizumab is used, do not exceed more than 2 doses in a 24-hour period
		• If CRS is refractory to 2 doses of tocilizumab, initiate/ increase dose of corticosteroids and consider alternative anti-cytokine therapy.
		• If suspicion of ICANS is concurrent with CRS, choose alternative to tocilizumab.
		• If no clinical improvement in signs and symptoms of CRS with tocilizumab:
		  • Consider siltuximab, 11 mg/kg iv over 1 hour, one time only, or
		  • Consider anakinra, 100 mg sc once/day
			Recommend dexamethasone 10 - 20 mg iv every 6 hours (or equivalent).
			Note: If suspicion of ICANS is concurrent with CRS, initiation of dexamethasone is highly recommended (see Neurotoxicity guidelines in Appendix E).
				Improving
				• Discontinue anti-cytokine therapy
				• Taper corticosteroids
				Manage as above
				Not improving
				• Manage as grade 4 (below)

CRS Grade[a]	Supportive Care	Anti-cytokine Therapy[b]	Corticosteroids	follow-up
Grade 4: Life-threatening symptoms Fever ≥ 38.0° with hypotension requiring ≥ 2 or high dose vasopressors excluding vasopressin Requirements for ventilator support and/or continuous renal replacement therapy or other hemodialysis procedures Consider and assess for development of MAS/HLH[c], including monitoring of fibrinogen and triglyceride levels	Permanently discontinue epcoritamab for grade 4 CRS In-person evaluation by a medical professional, ideally at site or center with experience managing CRS. Evaluate for other causes of fever and initiate broad spectrum antibiotics per local guidelines to continue until fever resolves; in the case of concurrent febrile neutropenia, follow local guidelines until febrile neutropenia resolves. Manage in Intensive Care Unit with: IV fluids as indicated Vasopressor support as indicated Mechanical ventilation and/or renal replacement therapy may be required	Recommended (refer to notes) Example: Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) Notes: • If tocilizumab is used, do not exceed more than 2 doses in a 24-hour period • If CRS is refractory to 2 doses of tocilizumab, initiate/ increase the dose of corticosteroids and consider alternative anti-cytokine therapy. • If suspicion of ICANS is concurrent with CRS, choose alternative to tocilizumab. • If no clinical improvement in signs and symptoms of CRS with tocilizumab: • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only, or Consider anakinra, 100 mg SC once/day	Recommend high-dose corticosteroids: • Dexamethasone 10-20 mg iv every 6 hours or Methylpredniso-lone 1 mg/kg iv BID	<u>Improving</u> • Discontinue anti-cytokine therapy • Taper corticosteroids Manage as above <u>Not improving</u> Consider alternative immune-suppressants (e.g., siltuximab, anakinra)

ASTCT	=	American Society for Transplantation and Cellular Therapy
BID	=	twice daily
CRS	=	cytokine release syndrome
HLH	=	hemophagocytic lymphohistiocytosis
ICANS	=	immune effector cell-associated neurotoxicity syndrome
IV	=	intravenously
MAS	=	macrophage activation syndrome
NC	=	nasal cannula;
NRB	=	nonrebreather
SC	=	subcutaneously
SmPC	=	summary of product characteristics
USPI	=	United States prescribing information

a) Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.
b) Refer to corresponding professional information for tocilizumab, siltuximab, or anakinra for details.
c) Anakinra should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids (Lehmberg K, Nichols KE, Henter JI, et al. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica. 2015;100(8):997-1004).

APPENDIX E: RECOMMENDED GUIDELINES FOR IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME (ICANS) GRADING AND MANAGEMENT

Table 14. ASTCT ICANS Consensus Grading for Adults:

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

ASTCT = American Society for Transplantation and Cellular Therapy
CTCAE = Common Terminology Criteria for Adverse Events
EEG = electroencephalogram
ICANS = immune effector cell-associated neurotoxicity syndrome
ICE = immune effector cell-associated encephalopathy
ICP = intracranial pressure
N/A = not applicable

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS. Grade 5 is considered to be fatal.
N/A indicates not applicable.

a) A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
b) Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).
c) Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v 5.0, but they do not influence ICANS grading.
d) Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v 5.0.

Source: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.

Table 15. Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool for Grading of ICANS (ICE Tool):

ICE Assessment	ICE Scoring:
Orientation: orientation to year, month, city, hospital: 4 points Naming: ability to name 3 objects (e.g., point to clock, pen, button): 3 points Following commands: ability to follow simple commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point Writing: ability to write a standard sentence (e.g., "The USA national bird is the bald eagle"): 1 point Attention: ability to count backwards from 100 by 10:1 point	10, no impairment 7-9, Grade 1 ICANS 3-6, Grade 2 ICANS 0-2, Grade 3 ICANS 0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

ICANS = immune effector cell-associated neurotoxicity syndrome
ICE = immune effector cell-associated encephalopathy

Source: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.

Table 16. Recommended Management Guidelines for Treatment of Neurotoxicity Associated with Immune Effector Cells:

Neurologic Toxicities	Supportive Care	Anti-cytokine Therapy	Corticosteroids	Follow-up
Grade 1: ICE score[a] 7-9 and/or depressed level of consciousness[b] but awakens spontaneously No seizures, motor weakness, or raised ICP/cerebral edema Confusion-mild disorientation Encephalopathy-mild limiting of ADLs Dysphasia-not impairing ability to communicate	Hold epcoritamab until resolution of event. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of event • Aspiration precautions • Recommend brain imaging and EEG per institutional guidelines	No CRS: not indicated Concurrent CRS only: • Choose alternative to tocilizumab (e.g., siltuximab, anakinra) • Anakinra should be considered in the event of neurotoxicity onset with ongoing CRS as well as neurotoxicity. • It should be given as a daily dose of 100 mg sc or 200 mg sc (100 mg Q12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. • Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment.	Dexamethasone, 10 mg iv Q12 hours	<u>Not improving</u> • Continue supportive care

Neurologic Toxicities	Supportive Care	Anti-cytokine Therapy	Corticosteroids	follow-up
Grade 2: ICE score[a] 3-6 and/or depressed level of consciousness but awakens to voice No seizures, motor weakness, or raised ICP/cerebral edema Somnolence-moderate, limiting instrumental ADLs Confusion-moderate disorientation Encephalopathy-limiting instrumental ADLs Dysphasia-moderate impairing ability to communicate spontaneously	Hold epcoritamab until resolution of event. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of event (e.g., levetiracetam) • Aspiration precautions • Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neurologic exams to include fundoscopy. Consider neurology consult. • Perform brain imaging (e.g., MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications	No concurrent CRS: • Anti-cytokine therapy not indicated Concurrent CRS: • Anakinra should be considered in the event of neurotoxicity onset with ongoing CRS as well as neurotoxicity. It should be given as a daily dose of 100 mg sc or 200 mg sc (100 mg Q12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg iv over 1 hour, one time only.	Dexamethasone at 10 - 20 mg iv every 12 hours	<u>Improving</u> • Discontinue anti-cytokine therapy if started • Taper corticoste-roids <u>Not improving</u>: • Manage as grade 3 (below)
Neurologic Toxicities	**Supportive Care**	**Anti-cytokine Therapy**	**Corticosteroids**	**Follow-up**

Grade 3: ICE score[a] 0-2 and/or depressed level of consciousness[b] but awakens to tactile stimulus Clinical seizure focal or generalized that resolves rapidly, or non-convulsive seizures on EEG that resolve with intervention No motor weakness Focal/local edema on neuroimaging Somnolence-obtundation or stupor Confusion-severe disorientation Encephalopathy-limiting self-care ADLs Dysphasia-severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	**First Episode:** epcoritamab interruption until full resolution. **Second episode:** permanently discontinue epcoritamab at the discretion of the investigator, if clinically indicated.	No concurrent CRS: • Anti-cytokine therapy not indicated. Concurrent CRS: • Anti-cytokine therapy indicated. • Anakinra should be considered in the event of neurotoxicity onset with ongoing CRS as well as neurotoxicity. It should be given as a daily dose of 100 mg sc or 200 mg sc (100 mg Q12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg iv over 1 hour, one time only.	Dexamethasone 10 - 20 mg iv every 6 hours (or its equivalent of methylprednisolone if not available in this circumstance)	<u>Improving</u> • Discontinue anti-cytokine therapy • Taper corticoste-roids <u>Not improving:</u> • Manage as grade 4 (below)

Neurologic Toxicities	Supportive Care	Anti-cytokine Therapy	Corticosteroids	Follow-up
Grade 4: ICE score[a] 0 and patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between Deep focal motor weakness[c] such as hemiparesis or paraparesis Diffuse cerebral edema on neuroimaging[c]; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation	Permanently discontinue epcoritamab for grade 4 event. • Mechanical ventilation may be required • Consider imaging of spine for focal motor weakness • Lower intracranial pressure (ICP) by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema • Aggressive management of ICP with institutional standard of care	No concurrent CRS: • Anti-cytokine therapy not indicated. Concurrent CRS: • Anti-cytokine therapy indicated. • Anakinra should be considered in the event of neurotoxicity onset with ongoing CRS as well as neurotoxicity. • It should be given as a daily dose of 100 mg sc or 200 mg sc (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. • Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg iv over 1 hour, one time only.	High-dose cortico-steroids: methylpredniso-lone 1000 mg/day iv × 3 days (Equivalent dose of dexamethasone is 188 mg/day)	<u>Improving</u> • Taper corticoste-roids <u>Not improving:</u> • Consider alternate immune-suppressants (contact Medical Monitor)

ADL = activities of daily living
ASBMT = American Society for Bone Marrow Transplant
CRS = cytokine release syndrome
EEG = electroencephalogram

ICANS	=	immune effector cell-associated neurotoxicity syndrome
ICE	=	immune effector cell associated encephalopathy
ICP	=	intracranial pressure
IV	=	intravenously
Q	=	every

a) A subject with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
b) Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).
c) Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Note: ICANS grade is determined by the most severe domain event not attributable to any other cause. For example, a subject with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

Sources: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.
Neelapu SS. Managing the Toxicities of CAR T-Cell Therapy. Hematol Oncol. 2019;37 (Supp 1):48-52.

APPENDIX F: RECOMMENDED GUIDELINES FOR MACROPHAGE ACTIVATION SYNDROME/HEMOPHAGOCYTIC LYMPHOHISTOCYTOSIS MANAGEMENT

Table 17. Recommendations for Management of Macrophage Activation Syndrome/Hemophagocytic Lymphohistocytosis:

Supportive Care	Anti-cytokine Therapy, Corticosteroids, and Follow-Up Management Guidelines
Intensive supportive care is essential because of frequent life-threatening, severe manifestations at presentation. Appropriate broad-spectrum antiviral, antibacterial, antifungal prophylaxis, and treatment must be initiated. The elimination of triggers (particularly infection) is crucial to remove the stimuli that initiate the abnormal immune system activation.	Suspected MAS/HLH • Withhold study treatment. • Consider subject referral to a hematologist. • Initiate supportive care, including intensive care monitoring, and appropriate therapy if indicated per institutional guidelines or published references[a] Confirmed MAS/HLH • Withhold study treatment. • Refer subject to a hematologist. • Initiate supportive care, including intensive care monitoring, and appropriate therapy if indicated per institutional guidelines or published references[a] • Subjects may resume epcoritamab only if: The subject has fully recovered from MAS/HLH Continued treatment is deemed to have a favorable benefit-risk ratio Approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. The supportive management of MAS/HLH is generally similar to that of cytokine-release syndrome: First line treatment: includes IL-6R-blockade with tocilizumab unless tocilizumab was already administered for the management of CRS. Corticosteroids are also indicated for the initial treatment of MAS/HLH, irrespective of the cause (CRS grade 4 treatment recommendations should be followed). Second-line treatment: Anakinra should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids. Anakinra should be given until resolution of CRS with a daily dose of 100 mg sc. In more severe CRS cases, especially if combined with MAS/HLH and/or neurotoxicity, anakinra 100 mg twice daily (every 12 hours) sc should be given until resolution of CRS and other concurrent T-cell toxicities, like neurotoxicity and/or MAS/HLH which could benefit from anakinra treatment. In case of rapidly progressing clinical course with ongoing CRS, anakinra should be administered as first line treatment. In more severe MAS/HLH cases, especially if combined with CRS and/or neurotoxicity, anakinra 100 mg sc twice daily should be given until resolution of MAS/HLH, which could benefit from anakinra treatment. -Anti-IL-6 antibody, siltuximab, might be considered as second line therapy

CRS = cytokine release syndrome
HLH = hemophagocytic lymphohistiocytosis
SC = subcutaneously

a) Schram AM and Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood. 2016;125(19):2908-1

APPENDIX G: GUIDELINES FOR CLINICAL TUMOR LYSIS SYNDROME

Table 18. Definitions of Laboratory and Clinical Tumor Lysis Syndrome (Howard Criteria):

Metabolic Abnormality	**Criteria for Classification of Laboratory Tumor Lysis Syndrome**	**Criteria for Classification of Clinical Tumor Lysis Syndrome**
Hyperuricemia	Uric acid > 8.0 mg/dL (475.8 µmol/L) in adults	
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.55 mmol/L) in adults	
Hyperkalemia	Potassium > 6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/L) or ionized calcium < 4.5 mg/dL (1.12 mmol/L)[a]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury[b]	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) (or a single value > 1.5 × the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output < 0.5 mL/kg/hr for 6 hrs

a) The corrected calcium level in mg/dL = measured calcium level in mg/dL + 0.8 × (4-albumin in g/dL).
b) Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg/dL (26.5 µmol/L) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the subject has clinical tumor lysis syndrome.

Note: In laboratory tumor lysis syndrome, 2 or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.
Source: Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.

Table 19. Cairo-Bishop Criteria for Clinical Tumor Lysis Syndrome and Grading:

Complication	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine	1.5 × ULN	> 1.5–3.0 × ULN	> 3.0-6.0 × ULN	> 6.0 × ULN	Death
Cardiac arrhythmia	Intervention not indicated	Non-urgent medical intervention needed	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	
Seizure	None	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	

ADL = activities of daily living

CHF = congestive heart failure

ULN = upper limit of normal

Source: Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78

Table 20. Recommendations for initial management of electrolyte imbalances and prevention of clinical tumor lysis syndrome:

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1hour. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise, re-check in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis syndrome. • At the discretion of the investigator, may re-check prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be re-checked within 24 hours.
Potassium ≥ ULN and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour and consider repeating every hour. • Perform ECG and consider commence telemetry. • Consider nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Consider administration of kayexalate up to 60 g per day (in divided doses or resonium A 60 g). • Consider administration of furosemide 20 mg IV × 1. • Consider administration of insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Consider administration of sodium bicarbonate 1 – 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Consider administration of calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate.

Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (dose per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 – 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin is low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour.

	• If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis syndrome.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1 – 2 hours.

APPENDIX H: BIOMARKER RESEARCH ACTIVITY WITHIN THE STUDY

Table 21. Biomarker research within the study:

Biomarker(s)	**Blood Volume**	**Sample/Test**	**Time points regarding application of study drugs**
TBNK (by flow cytometry)	3 mL EDTA	EDTA peripheral blood – Flow Cytometry	Loncastuximab tesirine: C1D1 pre-dose Epcoritamab: C1D1 pre-dose C2D1 pre-dose C3D1 pre-dose C6D1 pre-dose C9D1 pre-dose C13D1 pre-dose EOT, or in case of relapse/progression, or subject discontinuation, whichever comes first
Immuno-phenotyping (Exploratory)	20mL EDTA for PBMC isolation T-Cell metabolic fitness for selected subjects	Storage in liquid nitrogen	Loncastuximab tesirine: C1D1 pre-dose Epcoritamab: C1D1 pre-dose C2D1 pre-dose C3D15 pre-dose C5D1 pre-dose EOT, or in case of relapse/progression, or subject discontinuation, whichever comes first

Whole blood (ctDNA) (MRD)	10 mL Plasma	Plasma (ctDNA)	Loncastuximab tesirine: C1D1 pre-dose Epcoritamab: C2D1, C3D1, C6D1, C13D1 EOT, or in case of relapse/progression, or subject discontinuation, whichever comes first

C = cycle
ctDNA = circulating tumor DNA
D = Day
DNA = deoxyribonucleic acid
EDTA = ethylenediamine tetra acetic acid
MRD = minimal residual disease
TBNK = T-cells, B-cells, and natural killer cells

a) A sample should be drawn prior to all 4 doses (i.e., priming, intermediate, and 2 full doses) as part of a re-priming schedule.

Notes: Pre-dose sample should be collected prior to administration of any study medication, including premedication.