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 6 cycles subsequently (max. 8 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

	disease progression or relapse, unacceptable toxicity, death, major protocol deviation, pregnancy, patient or investigator decision. 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) - BORR after 18- and 24-months of treatment - 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 - BORR after 18- and 24-months of treatment - Progression rate - Relapse rate - Outcomes according to biological characteristics of DLBCL **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 35 institutions will be included with sites active in the German Lymphoma Alliance (GLA) (31 institutions) and the Italian Study Group Fondazione Italiana Linfomi (FIL) (4 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). 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. **<u>Contraception:</u>** 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. **<u>Adequate baseline organ function tests should be collected no more than 7 days before starting study treatment. The following criteria should be met:</u>** 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).

	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 concomintant 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). 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 8 cycles if no disease progression or relapse, unacceptable safety and tolerability, death, major protocol deviation, or patient, investigator, or sponsor decision in the meantime. Epcoritamab will be administered until 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. The data will also be submitted to CTIS. 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: Q3/2025 Last patient in: Q1/2027 Planned overall duration of the study: 4.5 years
Financial support:	AbbVie Sobi