CLINICAL TRIAL PROTOCOL

PRIME-CAR

AXICABTAGENE CILOLEUCEL CAR T-CELLS IN PATIENTS WITH RELAPSED OR REFRACTORY PRIMARY MEDIASTINAL B-CELL LYMPHOMA

Study sponsored by:
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FINANCIAL SUPPORT	Kite/Gilead

Version and date of Protocol: Version 1.2, March 12th 2025
EU-trial-number: 2024-510972-19-00

CONFIDENTIALITY STATEMENT

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1.2 Synopsis

Study title	AXICABTAGENE CILOLEUCEL CAR T-CELLS IN PATIENTS WITH RELAPSED OR REFRACTORY PRIMARY MEDIASTINAL B-CELL LYMPHOMA
Study name/code	PRIME-CAR
Identification (EU-Trial-Number)	2024-510972-19-00
Sponsor	Universität Münster Schlossplatz 2 48149 Münster
Protocol version	Version 1.2, March 12th, 2025
Phase and Study design	Prospective, multicenter, non-randomized, open-label, single-arm phase II study
Study population	40 patients are to be infused with axicabtagene ciloleucel.
Investigational Medicinal Product	Trade Name: Yescarta® Substance: Axicabtagene ciloleucel (iv) Manufacturer: Kite Pharma, Inc.
Coordinating investigator **Co-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 Univ.-Prof. Dr. med. Peter Dreger Innere Medizin V: Hämatologie, Onkologie und Rheumatologie Universitätsklinikum Heidelberg Im Neuenheimer Feld 410 69120 Heidelberg
Study Sites	24 Kite-certified sites in Germany

<table>
<tr><td>Background and Rationale</td><td>Patients who are refractory or relapse after first-line therapy of PMBCL have poor outcomes when treated with standard salvage therapy consisting of high-dose therapy and autologous stem cell transplantation (ASCT). Recent studies such as ZUMA-7 and real-world data on CAR T-cells in patients with early relapsed or refractory aggressive B-cell lymphoma, particularly DLBCL, showed improved EFS and OS with axicabtagene ciloleucel compared with the previous standard of care (SOC). These reports suggest comparable efficacy with similar toxicity profiles for CAR T-cells in PMBCL. However, larger studies with CAR T-cells in patients who are refractory to first-line therapy or who relapse after an initial response are urgently needed. This phase II study will evaluate the efficacy, safety and tolerability of second-line treatment with axicabtagene ciloleucel in PMBCL patients.</td></tr>
<tr><td colspan="2">Objectives and Endpoints:</td></tr>
<tr><td>Primary Objective(s)</td><td>Primary Endpoint(s)</td></tr>
<tr><td>• Evaluate the efficacy of axicabtagene ciloleucel in subjects with r/r PMBCL as measured by complete metabolic response (CMR) rate</td><td>CMR rate at 3 months from axicabtagene ciloleucel infusion based on disease assessment by PET-CT or PET-MRI according to Deauville criteria and Lugano Classification (Appendices 9-10).</td></tr>
<tr><td>Secondary Objectives(s)</td><td>Secondary Endpoint(s)</td></tr>
<tr><td>• Characterize the safety profile of axicabtagene ciloleucel in subjects with r/r PMBCL, in particular cytokine-release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)
• Further evaluate the efficacy of axicabtagene ciloleucel in subjects with r/r PMBCL</td><td>• Safety: Incidence of adverse events (AEs), serious adverse events (SAEs), and toxicities (CTCAE)
• Efficacy endpoints:
o CMR rate at 12 months (Lugano criteria)
o Best response rate (BRR: CR, PR)
o Overall survival (OS)
o Modified OS (mOS)
o Progression-free survival (PFS)
o Modified PFS (mPFS)
o PFS in responders
o Event-free survival (EFS)
o Modified EFS (mEFS)
o Relapse rate
o Best response during 2 years from axicabtagene ciloleucel infusion
o Time to first response</td></tr>
</table>

	○ Duration of complete metabolic response (DOCMR) ○ Partial response (PR) ○ Outcome according to biological characteristics of the lymphoma
Exploratory Objectives	**Exploratory Endpoints**
• Assess the pharmacokinetics/pharmacodynamics (PK/PD) of axicabtagene ciloleucel • Assess the effect of axicabtagene ciloleucel on patient-reported outcomes (PROs) and health-related quality of life (QoL)	Exploratory analyses: • Blood tests: LDH, CAR T-cell levels, ctDNA, cytokines and chemokines • Immunohistochemistry: CD19 and FOX-P3 frequency • Tumor: Bulk RNA-sequencing and whole exome sequencing of tumor and germline • QoL: physical functioning (assessed with the EORTC QLQ-C30), physical condition/fatigue (assessed with the EQ-5D-5L)
Duration of the study	Study set up: Q4/2024 First subject in: Q1/2025 Last subject in: Q1/2027 Last patient last treatment: Q1/2027 Last patient out: Q1/2029 All sites closed: Q2/2029 Duration of the study approx. 48 months
Inclusion criteria	1. Signed written informed consent form (ICF) according to ICH/EU GCP and national regulations 2. Age $\geq$ 18 years 3. ECOG performance status $\leq$ 2 4. Histologically confirmed primary mediastinal B-cell lymphoma (PMBCL) • based on the 2022 World Health Organization (WHO) (R. Allagio et al.) • classification by local pathology laboratory assessment 5. Patients must have received adequate first-line therapy including: • An anti-CD20 monoclonal antibody (rituximab), and • CHOP or CHOP-like chemotherapy Note: CHOP-like chemotherapy corresponds to CHOEP, ACVBP or EPOCH or COPADEM. Patients who received dose-reduced CHOP (e.g., mini-CHOP) are excluded except for dose reductions of vincristine due to peripheral neuropathy. Patients who have received additional

	drugs in combination with CHOP or CHOP-like regimen are eligible. 6. Relapsed or refractory disease after first-line chemoimmunotherapy, documented by PET-CT: • Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven relapse • Refractory disease defined as: ▪ Progressive disease (PD) during first-line therapy ▪ Stable disease (SD) as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP) and biopsy-proven residual disease, or ▪ Partial response (PR) as best response after at least 6 cycles, and biopsy-proven residual disease 7. At least 2 weeks must have elapsed since any prior systemic cancer therapy at the time the patient provides consent 8. Lymphoma tissue at recurrence available for central pathologic examination, exploratory endpoints, and ancillary studies (detailed sample collection requirements are described in protocol section 8.2) 9. Patients must have at least 1 measurable lesion per the Lugano Classification on anatomical imaging such as computed tomography (CT) imaging (functional imaging such as PET may not be used to identify a measurable lesion). A measurable lesion is defined as greater than 1.5 cm LDi for lymph node and greater than 1.0 cm LDi for extranodal lesions 10. Patients must be eligible for CAR T-cells as defined by: • Patient deemed eligible for CAR T-cells therapy by the study physician • Adequate vascular access for leukapheresis procedure (either peripheral or central venous line) 11. Adequate bone marrow, renal, hepatic, cardiac and pulmonary function defined as: • Absolute neutrophil count (ANC) ≥ 1000 cells/µL • Absolute lymphocyte count > 100/µL

	• Platelets ≥ 75,000 cells/µL • Creatinine clearance (as estimated by Cockcroft Gault) ≥ 40 ml/min • Transaminases (AST and ALT) <2.5 x ULN • Total bilirubin < 1.5 x ULN unless other reason known (Gilbert-Meulengracht-Syndrome in which 3 x ULN would be acceptable) • Left ventricular ejection fraction (LVEF) ≥ 40% and no evidence of clinically significant pericardial effusion, and no significant abnormal electrocardiogram (ECG) findings • Baseline oxygen saturation > 92% on room air 12. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 12 months are not considered to be of childbearing potential) 13. Sexually active men and FCBP must agree to use one of the highly effective contraceptive methods (combined oral contraceptives using two hormones, contraceptive implants, injectables, intrauterine devices, sterilized partner) together with one of the barrier methods (latex condoms, diaphragms, contraceptive caps) while on study; this should be maintained for 12 months after the last dose of study drug 14. Willingness not to drive a vehicle for 8 weeks post CAR T-cell treatment
Exclusion criteria	1. Patients who received more than one prior line of systemic therapy 2. Prior CD19-targeted therapy 3. History of another primary malignancy that has not been in remission for at least 2 years (except for non-melanoma skin cancer or carcinoma in situ (e.g., cervix, bladder, breast). A maintenance treatment is not allowed 4. History or presence of non-malignant CNS disorder, such as seizure disorder requiring anti-convulsive therapy, cerebellar disease, any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome (PRES), or cerebral edema with confirmed

	structural defects by appropriate imaging. History of stroke or transient ischemic attack within 12 months prior to enrollment. • Secondary CNS involvement of PMBCL is not an exclusion criterion 5. History of acute or chronic active hepatitis B or C infection. If there is a positive history of treated hepatitis B or hepatitis C, the viral load must be undetectable per quantitative polymerase chain reaction (PCR) and/or nucleic acid testing 6. Positive for human immunodeficiency virus (HIV) unless taking appropriate anti-HIV medications, with an undetectable viral load by PCR and with a CD4 count > 200 cells/µl 7. Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal catheter). Dedicated venous access catheters, such as a Port-a-Cath or Hickman catheter, are permitted 8. Uncontrolled systemic fungal, bacterial, viral or other infection despite appropriate antimicrobials at the time of enrollment 9. Presence of cardiac atrial or ventricular lymphoma involvement 10. History of any one of the following cardiovascular conditions within the past 12 months: Class III or IV heart failure as defined by the New York Heart Association, cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease 11. History of any medical condition including but not limited to autoimmune disease (e.g., Crohn's disease, rheumatoid arthritis, systemic lupus) requiring systemic immunosuppression and/or systemic disease modifying agents within the last year. Endocrine conditions that require maintenance with physiologic dose steroids are allowed 12. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography (CT) scan at screening. History of radiation pneumonitis in the radiation field (fibrosis) is allowed

	13. History of severe immediate hypersensitivity reaction to any of the agents used in this study, including aminoglycosides, cyclophosphamide, fludarabine or tocilizumab 14. Treatment with a live, attenuated vaccine within 6 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study 15. FCBP who are pregnant or breastfeeding 16. In the investigator's judgment, the patient is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation 17. Adult person unable to provide informed consent because of intellectual impairment, any serious medical condition, laboratory abnormality or psychiatric illness. 18. Simultaneously active participation in another clinical trial involving an IMP within 30 days prior to enrolment into this clinical trial 19. Patients with a physical or psychiatric condition which at the investigator's discretion may put the patient at risk, may confound the trial results, or may interfere with the patient's participation in this clinical trial 20. Known or persistent abuse of medication, drugs or alcohol 21. Primary immunodeficiency 22. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment 23. Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow up schedule
Study treatment	While completing the screening process corticoid therapy may be continued up 7 days prior to leukapheresis. After leukapheresis, one cycle of any therapy can be given as bridging therapy to reduce tumor burden if clinically necessary. A PET-CT-based staging after bridging therapy is optional. LD consists of lymphocyte depleting chemotherapy with fludarabine and cyclophosphamide (FC) applied on day -5 to day -3 followed by administration of axicabtagene ciloleucel on day 0. Patients will be observed

	as inpatients until at least day 10. Once the patient is discharged, outpatient visits including PET-CT-based staging are required on day 30 (±2 days), day 100 (±7 days), month 6 and 12 after axicabtagene ciloleucel administration. See study flow chart in chapter 8.1.
Assessment schedule	**Screening visit:** Patients will undergo a screening prior to any treatment to verify study eligibility within 28 days of enrollment. **Treatment period:** Patients receive a study visit on the first day of leukapheresis. The next study visit should take place on the first day of bridging chemotherapy, if this is carried out. If bridging therapy was administered a PET-CT prior to LD is optional. Study visits are then required on day -5 during LD and on day 0, the day of CAR T-cell infusion, and daily from day 1 to day 10 during inpatient observation. **Follow-up visits and restaging:** Outpatient study visits including new PET-CT scans are repeated on day 30 (±2 days), day 100 (±7 days) and at months 6 and 12. Final study visits are only required at Months 15, 18, 21 and 24. All study visits include a physical examination and laboratory tests. See tables A and B in section 8.2
Statistical consideration	The CR rate, PR rate, best response rate and relapse rate will be documented together with the corresponding 95% confidence intervals (Clopper-Pearson). Data on time to events (PFS, OS, EFS, best response during 2 years, time to first response) will be analyzed using Kaplan-Meier curves. Rates will be presented with 95% confidence intervals. For qualitative endpoints (AEs, SAEs) frequency tables will be prepared. Quantitative endpoints (laboratory parameters, cumulative doses of drugs, duration of therapy, duration of CR, duration of best response) will be described in tables displaying sample size, range, mean and standard deviation or medians and quartiles.

Study flow chart