STUDY SYNOPSIS

Study KT-US-471-0119
Kite Pharma, Inc.
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USA

Title of Study: A Phase 1/2 Open-label, Multicenter Study of Lenzilumab and Axicabtagene Ciloleucel in Subjects with Relapsed or Refractory Large B-cell Lymphoma
Investigators: Multicenter Study
Study Centers: This study enrolled subjects at 2 sites in the United States.
Publications: Kenderian, S. S., Oluwole, O. O., Mccarthy, P. L., Reshef, R., Shiraz, P., Ahmed, O., Le Gall, J., Nahas, M., Tang, L. And Neelapu, S. S. Zuma-19: A Phase 1/2 Multicenter Study of Lenzilumab Use With Axicabtagene Ciloleucel (Axi-Cel) In Patients (Pts) With Relapsed Or Refractory Large B Cell Lymphoma (R/R Lbcl). Blood 136(Supplement 1): 6-7, (2020). Conference Proceedings. Olalekan O. Oluwole, MBBS, Saad S. Kenderian, MD, Parveen Shiraz, MD, Reem Karmali, MD, MSc, Ran Reshef, MD, MSc, Philip L. McCarthy, MD, Nilanjan Ghosh, MD, PhD, Aleksandr Lazaryan, MD, PhD, MPH, Simone Filosto, PhD, Soumya Poddar, PhD, Daqin Mao, PhD, Andrew Peng, MS, Adrian Kilcoyne, MD, MPH, Myrna Nahas, MD, Sattva S. Neelapu, MD. A Phase 1/2 Study of Axicabtagene Ciloleucel Plus Lenzilumab in Patients With Relapsed or Refractory Large B-Cell Lymphoma. American Society of Hemotology; Dec 10-13, 2022; New Orleans, LA. Abstract 4635
Study Period: 04 June 2020 (First Subject Enrolled) 21 January 2021 (Last Subject Enrolled) 09 May 2022 (Last Observation [Data Cutoff Date] for this Report)
Phase of Development: Phase 1/2

Objectives:

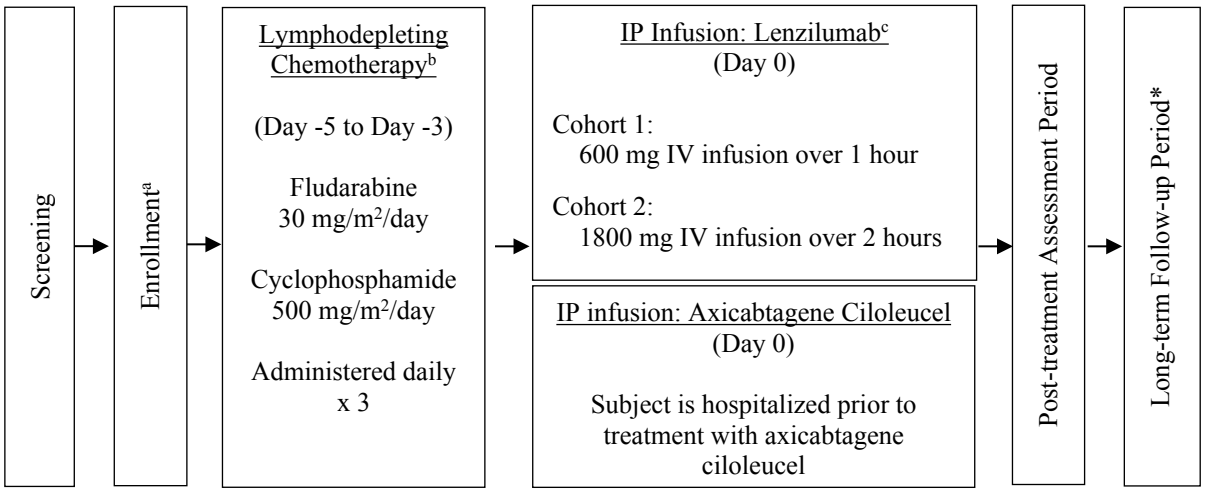
Phase 1: Evaluate the safety of sequenced therapy with lenzilumab and axicabtagene ciloleucel in subjects with refractory large B-cell lymphoma

Phase 2: Evaluate the incidence of Grade 2 or higher neurologic events with sequenced therapy given at the recommended Phase 2 dose of lenzilumab in subjects with relapsed or refractory large B-cell lymphoma

Secondary objectives were to Evaluate the safety and efficacy of sequenced therapy, Evaluate the extent of GM-CSF axis suppression in the blood, and to evaluate levels of chimeric antigen receptor (CAR) T cells and cytokines in the blood.

Methodology: ZUMA-19 is a Phase 1/2, open-label, multicenter study evaluating lenzilumab use to prevent axicabtagene ciloleucel treatment-related toxicity in subjects with relapsed or refractory large B-cell lymphoma. The addition of lenzilumab to the approved axicabtagene ciloleucel treatment regimen will hereafter be referred to as sequenced therapy. ZUMA-19 is separated into 2 distinct phases designated as the Phase 1 study and Phase 2 study.

In Phase 1, a 3+3 design was to be used to determine the recommended Phase 2 dose (RP2D) of lenzilumab within sequenced therapy for large B-cell lymphoma. There were to be 2 dose escalation cohorts. The RP2D of lenzilumab was to be determined primarily by clinical assessment of the incidence of dose limiting toxicities (DLTs) related to sequenced therapy. In addition to evaluation of DLT incidence, the extent of GM-CSF axis suppression as assessed by translational analysis may be assessed in defining the RP2D. A schema for Phase 1 of the study is provided below.



Abbreviations: CAR, chimeric antigen receptor; IP, investigational product; IV, intravenous

a Collection of peripheral blood mononuclear cells from the subjects will occur through leukapheresis performed at study enrollment.

b Lymphodepleting chemotherapy consists of administration of fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 for 3 consecutive days (Day -5 through Day -3).

c Investigational products: Lenzilumab will be administered on Day 0 at a dose determined by dose cohort as above 6 hours prior to axicabtagene ciloleucel infusion. Axicabtagene ciloleucel consists of a single IV infusion of a target of

2×10^6 anti-CD19 transduced autologous CAR T cells/kg (maximum dose 2×10^8 anti-CD19 transduced autologous CAR T cells) administered on Day 0.

*After the end of KT-US-471-0119, subjects who received an infusion of axicabtagene ciloleucel will complete the remainder of the 15-year follow-up assessments in a separate Long-term Follow-up study, KT-US-982-5968.

During Phase 1, a safety review team (SRT) was to pause enrollment to review safety data after 3 and 6 (as needed) subjects had been followed for 28 days after axicabtagene ciloleucel administration in each dose escalation cohort. At the conclusion of dose escalation, the SRT was to determine the RP2D and study conversion to Phase 2.

In Phase 2, the study was to assume a Simon 2-stage design. After 14 subjects had been treated with sequenced therapy at the RP2D of lenzilumab and followed for 28 days across Phase 1 and Phase 2, futility of sequenced therapy to demonstrate a significant decrease, compared to historical controls, in the incidence of Grade 2 or higher neurologic events was to be assessed. If the futility threshold was not met, an additional 16 subjects were to be treated with sequenced therapy at the RP2D of lenzilumab to complete accrual.

In total, this Phase 1/2 study was to enroll approximately 36 subjects to evaluate the incidence of Grade 2 or higher neurologic events related to sequenced therapy.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 36 subjects overall, with approximately 3 to 12 subjects in Phase 1 of the study and approximately 8 to 24 subjects in Phase 2. However, the sponsor terminated enrollment in the study earlier than planned, and thus the study did not proceed to Phase 2.

Analyzed: the numbers of subjects enrolled/leukapheresed and infused with sequenced therapy in Phase 1 are shown by cohort below.

	Cohort 1 (N=3)	Cohort 2 (N=3)	Overall (N=6)
Full analysis set[a], n (%)	3 (100)	3 (100)	6 (100)
Safety analysis set[b], n (%)	3 (100)	3 (100)	6 (100)
DLT evaluable set[c], n (%)	3 (100)	3 (100)	6 (100)

Data cutoff date: 09May2022.

Note: There are 9 subjects screened and 6 enrolled.

a The full analysis set consists of all enrolled subjects.

b The safety analysis set is defined as all subjects treated with any dose of axicabtagene ciloleucel and/or lenzilumab.

c The DLT analysis set is defined as all Phase I subjects that (a) received the target dose of lenzilumab (within ±10% of the planned dose) and axicabtagene ciloleucel (within ±20% of the planned dose) and were followed for at least 28 days after the anti-CD19 CAR T-cell infusion, or (b) received a dose of lenzilumab lower than for that cohort the target and experienced a DLT during the 28-day after the anti-CD19 CAR T cell infusion.

Diagnosis and Main Criteria for Inclusion: Subjects eligible for enrollment in the study were to be diagnosed with large B-cell lymphoma, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL). Subjects must have had relapsed disease after 2 or more lines of systemic therapy, OR chemorefractory disease.

Key Inclusion Criteria:

- Age ≥ 18 years
- At least 1 measurable lesion according to the International Working Group (IWG) Lugano Classification. Lesions that had been previously irradiated were considered measurable only if progression had been documented following completion of radiation therapy
- Magnetic resonance imaging of the brain showed no evidence of CNS lymphoma
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function

Key Exclusion Criteria:

- History of malignancy other than non-melanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) or FL unless disease free for at least 3 years
- History of Richter's transformation of chronic lymphocytic leukemia
- Autologous stem cell transplant (ASCT) within 6 weeks of planned axicabtagene ciloleucel infusion, history of allogeneic stem cell transplantation, or prior CD19 targeted therapy or prior CAR T-cell therapy
- History of autoimmune disease resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years before enrollment
- History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months before enrollment
- Presence of fungal, bacterial, viral, or other infection. Live vaccine ≤ 6 weeks prior to planned start of lymphodepleting regimen

Duration of Treatment: The study includes a 28-day screening period, leukapheresis, an optional 5-day bridging treatment period, a 3-day lymphodepleting chemotherapy treatment period, lenzilumab and Axicabtagene ciloleucel sequenced treatment, post-treatment assessment period (Day 1 to Month 3) and a LTFU period (> Month 3 through up to 15 years after sequenced therapy for safety and survival surveillance). Subjects were considered to be enrolled in the study when they commenced leukapheresis.

The study duration for individual subjects varies depending on their screening requirements, response to treatment, survival, and if applicable, timing of transition to the separate LTFU study.

Test Product, Dose, and Mode of Administration:

Lymphodepleting chemotherapy:

Lymphodepleting chemotherapy was to consist of cyclophosphamide 500 mg/m^2/day and fludarabine 30 mg/m^2/day for 3 days, prior to axicabtagene ciloleucel infusion.

Investigational product treatments:

Lenzilumab treatment was to consist of an intravenous (IV) infusion on Day 0, 6 hours prior to axicabtagene ciloleucel, in the following dose cohorts:

- Cohort 1: 600 mg IV administered on Day 0
- Cohort 2: 1800 mg IV administered on Day 0

Axicabtagene ciloleucel treatment was to consist of a single infusion of CAR transduced autologous T cells administered IV on Day 0 at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 ant-CD19 CAR T cells was to be administered.

Reference Therapy, Dose, Mode of Administration, and [Batch] No.: None

Criteria for Evaluation

Primary Endpoints:
Safety:

- Incidence of DLTs related to sequenced therapy with lenzilumab and axicabtagene ciloleucel (Phase 1)
- Incidence of Grade 2 or higher neurologic events within 28 days of axicabtagene ciloleucel administration (Phase 2)

Secondary Endpoints:
Safety:

- Incidence of AEs

Efficacy:

- Objective response rate (ORR)
- Complete response rate (CR)
- Duration of response (DOR)
- Progression free survival (PFS)
- Overall survival (OS)

Pharmacokinetics/Pharmacodynamics:

- Axicabtagene ciloleucel pharmacodynamics: levels of cytokines (including free GM-CSF) in blood
- Axicabtagene ciloleucel pharmacodynamics: levels of anti-CD19 CAR T cells in blood

Exploratory Endpoints:

Pharmacokinetics/Pharmacodynamics:

- Pharmacokinetics and pharmacodynamics of lenzilumab
- Immune profile related to the addition of lenzilumab to the axicabtagene ciloleucel regimen
- Levels of cytokines (including free GM-CSF), lenzilumab, anti-CD19 CAR T cells, T cells, and myeloid cells in the CSF

Statistical Methods:

Efficacy: The investigator assessment of disease status per the Lugano Classification {Cheson 2014} was used for disease response-related analyses.

CRR: CRR is defined as the incidence of CR per the IWG Lugano Classification as determined by the study investigators.

DOR: DOR was defined as the date of a subject's first objective response to disease progression per the IWG Lugano Classification {Cheson 2014} as determined by study investigators or death from any cause.

ORR: Objective response rate (ORR) was defined as the incidence of either a CR or a PR per the IWG Lugano Classification {Cheson 2014} as determined by the study investigators.

PFS: PFS was defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per the IWG Lugano Classification {Cheson 2014}, as determined by study investigators, or death from any cause.

OS: OS was defined as the time from axicabtagene ciloleucel infusion to the date of death. Subjects who had not died by the analysis data cutoff date were censored at their last date known as alive or the data cutoff date, whichever was earlier.

Pharmacokinetics/Pharmacodynamics: Pharmacokinetics (ie, levels of both lenzilumab and anti-CD19 CAR T cells in blood) were summarized descriptively for all subjects over time. Pharmacodynamic analysis included longitudinal measurements of serum analytes associated with the known mechanism of action of CAR T cells.

Safety: Safety analyses were to be conducted on the safety analysis set.

Treatment-emergent AEs (TEAEs) were defined as AEs with an onset on or after lenzilumab administration. AEs were to be coded with the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of all AEs were to be graded using the NCI CTCAE version 4.03. CRS events at the syndrome level were to be reported using a modification of the Lee grading scale {Lee 2014}. Individual CRS symptoms were to be graded using CTCAE version 4.03.

Overviews of the subject incidence of AEs occurring after enrollment (ie, commencement of leukapheresis) and possibly related to 1) the investigational products (lenzilumab and/or axicabtagene ciloleucel), 2) lymphodepleting chemotherapy, or 3) any protocol-required study procedure were to be summarized. All TEAEs, Grade 3 or higher TEAEs, treatment-related TEAEs, SAEs, and TEAEs of interest (including identified and potential risks) were to be tabulated by preferred term (PT) and/or system organ class (SOC). Primary causes of deaths were to be summarized. Shifts in laboratory toxicity grades from the baseline assessment to the worst postbaseline assessment were to be summarized with descriptive statistics. The incidence of concomitant medications of interest was to be summarized.

A DLT was defined as the following sequenced therapy-related events with onset within the first 28 days following axicabtagene ciloleucel infusion:

- Grade 4 neutropenia lasting longer than 21 days from the day of cell transfer
- Grade 4 thrombocytopenia lasting longer than 28 days from the day of cell transfer

- Any sequenced therapy-related AE requiring intubation, including Grade 4 encephalopathy requiring intubation for airway protection
- Any sequenced therapy-related Grade 5 event

All other clinically significant Grade 3 toxicities lasting more than 3 days and all Grade 4 toxicities, with the exception of the conditions listed in the Protocol which were not considered DLTs.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 6 subjects were enrolled/leukapheresed in Phase 1, all of whom were treated with axicabtagene ciloleucel and lenzilumab. The 6 treated subjects comprised 3 subjects in each of the 2 planned dose escalation cohorts. Doses for dose escalation cohorts were either 600 mg (Cohort 1) or 1800 mg (Cohort 2) of lenzilumab prior to axicabtagene ciloleucel (2×10^6 anti CD19 CAR T cells/kg). Infusion of axicabtagene ciloleucel and lenzilumab was completed for all 6 subjects infused.

As of the data cutoff date for this report, all 6 subjects (100%) had the opportunity to be followed up for at least 14.7 months (range: 14.7 to 22.3 months) after infusion of axicabtagene ciloleucel and lenzilumab. The median follow-up time from infusion of axicabtagene ciloleucel and lenzilumab was 11.32 months (range: 3.6 to 21.7 months). Of the 6 enrolled subjects, 4 (67%) had died as of the data cutoff date for this report.

Among all subjects treated with sequenced therapy, the median age was 59.5 years (range: 51 to 80 years). All 6 subjects (100%) were male and white (6 subjects, 100%). Two subjects (33%) had Stage I disease, 2 subjects (33%) had Stage II disease, and 2 subjects (33%) had Stage III disease. Three subjects (50%) had histologically proven DLBCL arising from FL, and 3 subjects (50%) had DLBCL not otherwise specified. All subjects had at least 2 lines of prior therapies. In addition, one subject (17%) had prior radiotherapy with curative intent.

Efficacy Results: Of the 6 subjects infused with sequenced therapy, 4 subjects (67%) had CR as best response, 2 subjects from each cohort. One subject (17%) from dose Cohort 2 had a best response of PR 28 days after axicabtagene ciloleucel infusion. One subject from Cohort 1 had PD on Day 27.

The range of DOR for the subjects with CR or PR was 2.66 months to 12.12 months. One subject (17%) did not reach CR or PR and therefore did not have a DOR calculated.

As of the data cutoff date, the median PFS was 11.32 months and ranged from 0.92 months to 13.04 months.

As of the data cutoff date, 4 of the 6 subjects (67%) treated with lenzilumab and axicabtagene had died. Six subjects (100%) were alive at their 3-month follow-up. The cause of death for 3 subjects was COVID19 pneumonia, and 1 subject died due to PD. OS ranged from 3.58 months to 21.72 months, with a median OS of 11.32 months.

Pharmacokinetics/Pharmacodynamics Results:

Anti-CD19^{+} CAR T cells were detected in peripheral blood within 7 days after infusion in all subjects. The median time-to-peak was 8 days after the axicabtagene ciloleucel infusion. Among all subjects, the median peak CAR T-cell level was 28.35 cells/µL. Lenzilumab was detected in peripheral blood up to 4 weeks after infusion in all subjects, and there were consistently higher median levels of lenzilumab for subjects in cohort 2.

The median levels of 23 selected serum analytes changed by 2-fold or more between baseline and the peak level reached after infusion. Median time to peak was 3 days or more for all 23 analytes.

Safety Results: Sequenced therapy was not associated with any DLTs at any of the dose levels tested. All 6 subjects treated with sequenced therapy had at least 1 TEAE of Grade 3 or higher. All 6 subjects had TEAEs deemed to be related to axicabtagene ciloleucel, with Grade 4 as the highest severity for 1 subject (17%). All axicabtagene ciloleucel related-TEAEs resolved. Three subjects (50%) had SAEs, Grades 1 and 2 deemed related to axicabtagene ciloleucel, and all resolved within 3 days of onset. Three subjects (50%) experienced fatal TEAEs unrelated to sequenced therapy. No subjects had TEAEs related to lenzilumab treatment.

No subjects died within 30 days after lenzilumab and axicabtagene ciloleucel infusion. As of the data cutoff date for this report, 4 subjects (67%) had died more than 30 days after lenzilumab and axicabtagene ciloleucel infusion. Three of the 4 subjects died from COVID-19 pneumonia deemed unrelated to sequenced therapy, and 1 subject died from PD related to the primary malignancy.

CONCLUSIONS:

The conclusions from this analysis of Study KT-US-471-0119 are as follows:

- No DLTs were observed during Phase 1 of ZUMA-19.
- Of the 6 subjects infused with sequenced therapy, 4 subjects (67%) had best response of CR, 1 subject (17%) had a best response of PR, and 1 subject had PD.
- CAR T cells were detected in peripheral blood within the first 7 days after infusion with axicabtagene ciloleucel in all subjects. Lenzilumab was detected in peripheral blood at all time points collected through Week 4 after infusion in all subjects.
- Selected serum analyte levels presented in text had at least a 2-fold change between baseline and peak value.
- The main safety risks associated with ZUMA-19 were CRS and associated symptoms, neurologic events, infections, and cytopenias. Three subjects experienced Grade 5 TEAEs other than disease progression including 2 subjects with COVID-19 pneumonia and 1 subject with pneumonia (later clarified to also be related to COVID-19) that were deemed unrelated to treatment with sequenced therapy.