A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)

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The primary objective of Phase 1 is to evaluate the safety of KTE-X19.The primary objective of Phase 2 is to evaluate the efficacy of KTE-X19, as measured by the overall complete remission rate defined as complete remission (CR) and complete...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON54807

Source
ToetsingOnline

Brief title
ZUMA-3

Condition

- Leukaemias
- Leukaemias

Synonym
Acute Lymphoblastic Leukemia; Cancer of white blood cells.

Research involving
Human

Sponsors and support

Primary sponsor: Kite Pharma Inc.
Source(s) of monetary or material Support: Kite Pharma Inc.

Intervention

Keyword: Adult Acute Lymphoblastic Leukemia, Efficacy, KTE-X19, Safety

Outcome measures

Primary outcome

Primary Endpoint:

• Phase 1: Incidence of adverse events (AEs) defined as dose-limiting

toxicities (DLTs) in the DLT evaluable set

• Phase 2: Overall complete remission rate (CR + CRi) per independent

review (Appendix A) as defined by;

o Less than or equal to 5% blasts in the bone marrow, and

o No other evidence of morphologic disease*, and either

o Platelets >= 100,000/µL and ANC >=1,000/µL (CR) or

o Platelets < 100,000/µL and ANC >= 1000/µL or Platelets >= 100,000/µL and ANC <

1000/µL but not CR (CRi).

*All subjects must demonstrate a negative CSF assessment to be considered to

achieve CR or CRi. Subjects with extramedullary disease detected through

imaging at baseline also must meet the criteria for CR per Cheson 2007

(Appendix A of KTE-C19-103 study protocol) in order to be considered to have CR

or CRi.

Secondary outcome

Secondary Endpoints:

• Overall complete remission rate (CR + CRi) per investigator assessment

(Appendix A)

• Duration of Remission (DOR)

• Minimal Residual Disease (MRD) negative rate

• Allogeneic stem cell transplant (Allogeneic SCT) rate

• Overall survival (OS)

• Relapse-free Survival (RFS)

• Incidence of AEs and common terminology criteria for adverse events (CTCAE)

grade changes in safety laboratory values

• Incidence of anti-KTE-X19 antibodies

• Changes over time in the EQ-5D score and VAS score (phase 2 only).

Study description

Background summary

Acute lymphoblastic leukemia is a heterogeneous group of lymphoid disorders that results from the clonal proliferation of immature lymphocytes of B-cell or T-cell lineage in the blood, bone marrow, and other organs. The disease occurs with a bimodal age distribution, with 60% of cases diagnosed in subjects less than 20 years old, and 25% of cases diagnosed at age 45 years or greater.

While 5-year survival rates are 80-90% in children, less than 25% of adults achieve long-term survival, and the majority of the 1,400 ALL deaths per year in the United States are in adults (Siegel et al 2014; NCCN practice guidelines 2014). While initial CR rates in adults are high (80-90%) and the median duration of first remission in most studies is 18 months or longer, most subjects eventually experience relapse (Rowe et al 2014; Kantarjian et al 2004;

Larson et al 1995; Kantarjian et al 1994). Outcomes in the second-line and beyond setting with chemotherapy are poor with complete remission (CR) rates of approximately 20-40%, being lower in subjects with relapse within 12 months of initial response, and overall survival (OS) being approximately 6 months, making the relapsed/refractory setting the area of greatest unmet need in ALL (Fielding et al 2007; Tavernier et al 2007; Thomas et al 1999; O'Brien et al 2013; Faderl et al 2011; Kantarjian et al 2003).

As most advanced cancers eventually become refractory to conventional therapies, new treatment modalities are needed. Immunotherapy, which is based on the enhancement of an immune response against the tumour, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Studies with immune checkpoint inhibitors and tumour infiltrating lymphocytes have demonstrated the potential of T cells to treat cancer. T cells need to possess the appropriate specificity for a tumour, be present in sufficient numbers, and overcome any local immunosuppressive factors to be effective. Engineered T cells are a promising approach for cancer therapy (Kershaw et al 2013).

Engineered Autologous Cell Therapy (eACT*) is a process by which a patient*s own T cells are collected and subsequently genetically altered to recognize and target antigens expressed on the cell surface of specific malignancies (Kochenderfer et al 2013). The ability to genetically engineer human T cells and use them to mediate cancer regression in subjects has been demonstrated in a number of studies and has opened possibilities for the treatment of subjects with a wide variety of cancer types including B cell malignancies expressing the CD19 antigen. CD19 is a 95 kDa transmembrane protein expressed only in the B cell lineage. It is expressed in all normal B cells starting at the pre-B cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is maintained in B cell malignancies including all subtypes of B cell NHL, chronic lymphocytic leukemia (CLL) and non T cell acute lymphoblastic leukemia (ALL; Blanc et al 2011) with the exception of multiple myeloma. Although there have recent advances in novel therapies for these B cell malignancies (Wang et al 2013* Byrd et al 2013* Furman et al 2014) most subjects eventually develop resistance to approved therapies. Chimeric antigen receptor+ T cell therapy may circumvent mechanisms of resistance and potentially address the unmet medical need for these subjects.

An anti-CD19 CAR was generated at the Surgery Branch of the National Cancer Institute (NCI). This CAR contained the mouse anti-human single chain variable fragment (scFv) derived from the antibody FMC63, the CD3-zeta T cell activation domain, and a CD28 co-stimulatory domain. In preclinical models, the anti-CD19 CAR recognized and killed CD19+ target cells in vitro and in vivo. A phase 1 study of this anti-CD19 CAR has been conducted at the NCI using anti-CD19 CAR+ T cells generated by retroviral transduction and manufactured at the NCI. Lymphodepleting chemotherapy followed by infusion of anti-CD19 CAR+ T cells has

demonstrated durable responses in the majority of subjects with relapsed and refractory CLL, indolent NHL, diffuse large B cell lymphoma (DLBCL), and primary mediastinal B cell lymphoma (PMBCL) with the predominant toxicity of cytokine release syndrome (CRS). KTE-X19 utilizes the anti-CD19 CAR from the NCI and is produced through a streamlined, closed manufacturing process.

Two different manufacturing processes are used for Kite*s anti-CD19 CAR T cell products:
CLP and XLP. These 2 processes yield different products per FDA and EMA. The processes differ in lymphocyte enrichment and activation steps to address the needs of making products from patients with different tumor indications.
KTE-X19 is manufactured via the XLP manufacturing process for subjects that are characterized by having high numbers of CD19-expressing circulating tumor cells (B-cell acute lymphoblastic leukemia, CLL, and MCL). All clinical subject lots manufactured for ZUMA-3 use the XLP process. The introduction of the KTE-X19 code is an administrative name change and does not change the manufactured product.

Briefly, from the leukapheresis product the T cells in the harvested leukocytes are enriched by binding to magnetic beads coated with anti-CD4 and anti-CD8 antibodies. T-cells are activated by culturing with anti-CD3 and anti-CD28 antibodies, and are then transduced with a retroviral vector containing an anti-CD19 CAR gene. These engineered T cells are then propagated in culture to generate a sufficient number of cells for administration.

For the ZUMA-3 (KTE-C19-103) study, subjects with relapsed/refractory mantle cell lymphoma (r/r ALL) are to be studied within the phase I/II multi-center study evaluating the safety and efficacy of KTE-X19.

Study objective

The primary objective of Phase 1 is to evaluate the safety of KTE-X19.

The primary objective of Phase 2 is to evaluate the efficacy of KTE-X19, as measured by the overall complete remission rate defined as complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) in adult subjects with r/r ALL.

Secondary objectives will include assessing the safety and tolerability of KTE-X19 additional efficacy endpoints, and change in EQ-5D scores.

Study design

ZUMA-3 is a Phase 1/2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with relapsed or refractory B-precursor ALL. In this study, relapsed or refractory is defined as one of the following:

primary refractory; first relapse following a remission lasting <= 12 months; relapsed or refractory after second-line or higher therapy; relapsed or refractory after allogenic SCT (provided the transplant occurred >= 100 days prior to enrollment and that no immunosuppressive medications were taken <= 4 weeks prior to enrolment).

During phase 1, approximately 3-12 subjects with high burden [M3 marrow (>25% leukemic blasts) or >=1000 blasts/mm3 in the peripheral circulation] r/r ALL disease who are evaluable for DLT will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, and in collaboration with at least 1 study investigator, will review safety data and make recommendations regarding further enrollment in phase 1 or proceeding to phase 2 based on the incidence of DLTs and overall safety profile of KTE-X19. Additionally, up to approximately 40 subjects with high or low burden disease may be enrolled to further assess safety at a dose deemed to be tolerable by the SRT. See Figure 2 of Section 3.1 and Section 9.6 of the KTE-C19-103 study protocol for a schematic that illustrates Phase 1 dosing.

During phase 2, approximately 50 subjects in the mITT set will be assessed to evaluate the efficacy and safety of KTE-X19. Among these, the ratio of subjects with and without prior blinatumomab treatment will be approximately 15:35 (refer to Section 10.7.2). Prior blinatumomab is defined as at least 2 weeks of therapy. An independent Data Safety Monitoring Board (DSMB) will review safety data through one interim analysis during the Phase 2 portion of the study. In this interim analysis, the DSMB will review safety data after 20 Phase 2 subjects have been treated with KTE-X19 and had the opportunity to be followed for 30 days after the KTE-X19 infusion.

Intervention

KTE-C19-103 study will use the same lymphodepleting chemotherapy regimen consisting of fludarabine at a dose of 25 mg/m2/day IV over 30 minutes on Day -4, Day -3, Day -2 prior to KTE-X19 and cyclophosphamide at a dose of 900 mg/m2/day IV over 60 minutes on Day -2 prior to KTE-X19. Day -1 will be a rest day. To date, subjects have received doses of anti-CD19 CAR T cells ranging from 0.5 - 30 x 106 anti-CD19 CAR T cells/kg.

Study burden and risks

For a study treatment, the subject needs to be hospitalized for at least 7 days. Before KTE-Z19 infusion the subject will receive 3 days of chemotherapy. The subject may experience side effects after treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

101. Relapsed or refractory B-precursor ALL defined as one of the following:
o Primary refractory disease
o First relapse if first remission <= 12 months
o Relapsed or refractory disease after two or more lines of systemic therapy
o Relapsed or refractory disease after allogeneic transplant provided subject is at least 100 days from stem cell transplant at the time of enrollment and off of immunosuppressive medications for at least 4 weeks prior to enrollment
102. Morphological disease in the bone marrow (> 5% blasts)
103. Subjects with Ph+ disease are eligible if they are intolerant to tyrosine kinase inhibitor (TKI) therapy, or if they have relapsed/refractory disease despite treatment with at least 2 different TKIs
104. Age 18 or older
105. Eastern cooperative oncology group (ECOG) performance status of 0 or 1
106. ANC >= 500/uL unless in the opinion of the PI cytopenia is due to underlying leukemia and is potentially reversible with leukemia therapy
107. Platelet count >= 50,000/uL unless in the opinion of the PI cytopenia is

due to underlying
leukemia and is potentially reversible with leukemia therapy
108. Absolute lymphocyte count >= 100/µL
109. Adequate renal, hepatic, pulmonary and cardiac function defined as:
o Creatinine clearance (as estimated by Cockcroft Gault) >= 60 cc/min
o Serum ALT/AST <= 2.5 x ULN (upper limit normal)
o Total bilirubin <= 1.5 mg/dl, except in subjects with Gilbert*s syndrome.
o Left ventricular ejection fraction (LVEF) >= 50%, no evidence of pericardial effusion as determined by an
ECHO, no NYHA class III or class IV functional classification, and no clinically significant
arrhythmias
o No clinically significant pleural effusion
o Baseline oxygen saturation > 92% on room air
110. Females of childbearing potential must have a negative serum or urine pregnancy test
111. In subjects previously treated with blinatumomab, CD19 tumor expression on blasts obtained from bone marrow or peripheral blood must be documented after completion of the most recent prior line of therapy. If CD19 expression is quantified, then blasts must be >= 90% CD19 positive.

Exclusion criteria

201. Diagnosis of Burkitt*s leukemia/lymphoma according to WHO classification or chronic myelogenous leukemia lymphoid blast crisis
202. History of malignancy other than non-melanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) unless disease free for at least 3 years
203. History of severe hypersensitivity reaction to aminoglycosides or any of the agents used in this study
204. CNS abnormalities
a. Presence of CNS-3 disease, defined as detectable cerebrospinal blast cells in a sample of CSF with >= 5 WBCs per mm3 with or without neurological changes, and presence of CNS-2 disease defined as detectable cerebrospinal blast cells in a sample of CSF with <5 WBCs per mm3) with neurological changes
Note: Subjects with CNS-1 (no detectable leukemia in the CSF) and those with CNS-2 without clinically evident neurological changes are eligible to participate in the study.
b. History or presence of any CNS disorder such as a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome (PRES), or cerebral edema
205. History of concomitant genetic syndrome associated with bone marrow failure such as Fanconi anemia, Kostmann syndrome, Shwachman-Diamond syndrome or any other known bone marrow failure syndrome
206. History of myocardial infarction, cardiac angioplasty or stenting,

unstable angina, or other clinically significant cardiac disease within 12 months of enrollment
207. History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrollment.
208. Primary immunodeficiency
209. Known infection with HIV, hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive). A history of treated hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing.
210. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple UTI and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite medical monitor
211. Prior medication:
o Salvage systemic therapy (including chemotherapy, TKIs for Ph+ ALL and blinatumomab) within 1 week or 5 half-lives (whichever is shorter) prior to enrollment
o Prior CD19 directed therapy other than blinatumomab
o History of CTCAE grade 4 neurologic event or grade 4 CRS (Lee 2014) with prior CD19-directed therapy
o Treatment with alemtuzumab within 6 months prior to enrollment, clofarabine or cladribine within 3 months prior to enrollment, or PEG-asparaginase within 3 weeks prior to enrollment
o Donor lymphocyte infusion (DLI) within 28 days prior to enrollment
o Any drug used for GVHD within 4 weeks prior to enrollment (eg, calcineurin inhibitors, methotrexate, mycophenolyate, rapamycin, thalidomide), or immunosuppressive antibody used within 4 weeks prior to enrollment (eg, anti-CD20, anti-tumor necrosis factor, anti-interleukin 6 or anti-interleukin 6 receptor)
o At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy prior to enrollment (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists etc)
o Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to enrollment
212. Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Ommaya reservoirs and dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted
213. Acute GVHD grade II-IV by Glucksberg criteria or severity B-D by IBMTR index; acute or chronic GVHD requiring systemic treatment within 4 weeks prior to enrollment
214. Live vaccine <= 4 weeks prior to enrollment
215. Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the

fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential
216. Subjects of both genders of child-bearing potential who are not willing to practice birth control from the time of consent through 6 months after the completion of KTE-X19
217. In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.
218. History of autoimmune disease (e.g. Crohns, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-05-2019
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO

Date:	08-09-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	10-05-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-04-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-09-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-10-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-11-2018
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-12-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-04-2019
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Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-05-2019
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Application type:	Amendment
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Approved WMO	

Date:	09-12-2019
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Approved WMO Date:	26-05-2021
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-005009-35-NL
ClinicalTrials.gov	NCT02614066
CCMO	NL56913.000.16