# A Phase 1 Open-label, Multicenter Study Evaluating the Safety and Efficacy of KITE-363, an Autologous Anti-CD19/CD20 CAR T-cell Therapy, in Subjects With Relapsed and/or Refractory B-cell Lymphoma

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This study has been transitioned to CTIS with ID 2024-511616-24-00 check the CTIS register for the current data. Primary ObjectivesPhase 1a:• Evaluate the safety of KITE-363 in subjects with r/r B-cell lymphoma• Determine the dose level(s) for Phase...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Lymphomas non-Hodgkin's B-cell |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON53464

**Source**
ToetsingOnline

**Brief title**
KT-US-499-0150 (ICON 0035/0353)

### Condition

- Lymphomas non-Hodgkin's B-cell

**Synonym**
lymph node cancer, non-Hodgkin's B-cell lymphoma

**Research involving**

Human

## Sponsors and support

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

## Intervention

**Keyword:** CAR T-cell therapy, non-Hodgkin B-cell lymphoma

## Outcome measures

### Primary outcome

Primary Endpoints:

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

-limiting toxicities (DLTs)

Phase 1b: ORR (CR +PR) (per Lugano 2014)

Secondary Endpoints:

• Incidence of AEs and serious AEs (SAEs)

• TTNT, CR rate, DOR, PFS, and OS (per Lugano 2014 )

• Incidence of antibodies to KITE-363 CARs after the KITE*363 infusion

• Levels of analytes (including cytokines) and KITE-363 CAR T cells in the

blood after the KITE-363 infusion

### Secondary outcome

Exploratory Endpoints:

• Levels of cytokines, KITE-363 CAR T cells, T cells, and myeloid cells in the

CSF after treatment with KITE-363

• Presence and levels of CD19, CD20, and other B-cell antigens in relation to

the presence and activity of KITE-363

• Product characteristics of pre-infusion KITE-363

• Minimal residual disease (MRD) negative response rate

# Study description

**Background summary**

B-cell Lymphoma
B-cell lymphomas encompass a group of lymphoma subtypes categorized within the 2 broad categories non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), of which NHLs comprise the majority of diagnosed cases. The therapeutic landscape varies for each distinct tumor subtype, but in general, there are limited effective therapies in the relapsed and/or refractory (r/r) settings for B-cell lymphomas.

**Study objective**

This study has been transitioned to CTIS with ID 2024-511616-24-00 check the CTIS register for the current data.

Primary Objectives
Phase 1a:
• Evaluate the safety of KITE-363 in subjects with r/r B-cell lymphoma
• Determine the dose level(s) for Phase 1b dose expansion
Phase 1b:
• Evaluate the efficacy of KITE-363 in subjects with r/r B-cell lymphoma as measured by the objective response rate (ORR), defined as complete response (CR) plus partial response (PR) rates

Secondary Objectives
• Further characterize the safety profile of KITE-363 in subjects with r/r B-cell lymphoma (Phase 1b)
• Evaluate the efficacy of KITE-363 in subjects with r/r B-cell lymphoma as measured by time to next treatment (TTNT), CR rate, duration of response (DOR), progression-free survival (PFS), and overall survival (OS)
• Evaluate the immunogenicity of KITE-363
• Evaluate the pharmacokinetics and the pharmacodynamic effects of the KITE-363 treatment

Exploratory Objectives:
• Evaluate the tumor, bone marrow, and cerebrospinal fluid (CSF) microenvironments in relation to the presence and activity of KITE-363

**Study design**

This is a Phase 1, open-label, multicenter study evaluating the safety and efficacy of KITE-363 in subjects with r/r B-cell lymphoma. The study will comprise dose-escalation (1a) and dose-expansion (1b).

Phase 1a
The dose -escalation portion of the study will use a 3 + 3 study design. Up to 30 subjects with r/r large B-cell lymphoma (LBCL; including all subtypes in WHO 2016 {Swerdlow 2016} as well as transformed iNHL), r/r follicular lymphoma (FL), r/r marginal zone
lymphoma (MZL), r/r nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), or r/r B-cell lymphoma, unclassifiable (with features intermediate between diffuse large-B-cell lymphoma [DLBCL] and classical Hodgkin lymphoma [cHL]) will be enrolled and treated at the sequential dose-escalation levels and evaluated for DLTs. Additional disease types may be considered after discussion with participating investigators. There will be a maximum of 5 planned dose-escalation levels. Infusion of KITE-363 in subjects enrolled in Phase 1a will be staggered, as shown below, to allow for observations of acute and subacute toxicities:
• Dose -escalation Level 1: the second and third subjects in this dose-level cohort will receive the KITE-363 infusion at least 28 days after the previous subject has been dosed
• Dose escalation Levels 2 and 3: each of the first 2 subjects in these dose-level cohorts will receive the KITE-363 infusion at least 28 days after the previous subject has been dosed
• Dosing of the first subject in each dose-escalation level cohort will be at least 28 days after the last subject in the previous dose -escalation level cohort has completed the KITE-363 infusion.
At the end of each dose-escalation level cohort, all available safety data will be reviewed before the initiation of dosing at the next dose level.
A safety review team (SRT) will pause enrollment to review the safety data after 3 or 6 subjects have been enrolled in each dose-escalation level cohort and have had the opportunity to be followed for 28 days after infusion of KITE-363. In discussion with
the SRT, additional dose levels may be considered as part of the dose escalation.

Phase 1b
In order to further characterize the benefit/risk of the therapy, the sponsor may, in consultation with the SRT, choose to treat up to approximately 40 additional subjects at 1 or more dose-level cohorts (referred to as a dose-expansion cohorts) within different disease
indications. Each dose-expansion cohort will be opened only after the specific dose level has been evaluated in the corresponding doseescalation level cohort and deemed to be tolerable in consultation with the SRT. Dose-expansion cohorts

can enroll concomitantly with the dose-escalation level cohorts as long as the dose(s) has been deemed to be tolerable in consultation with the SRT. In order to review the safety data of the dose-expansion portion of the study, the SRT will meet after approximately 10, 20, and 30 subjects are enrolled in Phase 1b (across different expansion dose levels) and have had the opportunity to be followed for 28 days after infusion of KITE-363. The SRT may meet earlier or more frequently based on emerging safety data.
At the conclusion of Phase 1, the sponsor, in consultation with the SRT, will determine the recommended Phase 2 dose (RP2D). An amendment will subsequently be submitted etailing Phase 2 of the study.

**Intervention**

Subjects will receive 1 infusion of KITE-363. The duration of the study for individual subjects will vary depending on a subject*s response to treatment and survival. For a subject who completes the entire protocol from the date of informed consent through the completion of the long-term follow-up period, the duration of the study will take approximately 15 years to complete. The need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects.

**Study burden and risks**

This is a first-in-human study and therefore, there are no clinical data on the benefit/risk for
humans. At this stage of development, the evaluation of benefit to patients is ongoing and the
overall preliminary safety data from nonclinical studies does not show any unexpected or
significant safety findings.
The benefit/risks have been identified for 2 other Kite anti-CD19 CAR T-cell products,
axicabtagene ciloleucel and KTE-X19. The risks of axicabtagene ciloleucel and KTE-X19
therapy are well described. Two important identified risks, which are not commonly encountered in general oncology practice, include CRS and neurologic events. These events have an early onset, generally within 2 weeks after the therapy, and are mostly reversible (> 95%). Additional important identified risks include cytopenias, infection, and hypogammaglobulinemia. Some of the important potential risks associated with axicabtagene ciloleucel/KTE-X19 are replication-competent retrovirus, secondary malignancy, immunogenicity, and tumor lysis syndrome.
Strategies have been developed to monitor for and manage the risks associated with anti-CD19 CAR T-cell therapy and are included in the KITE-363 IB. The eligibility criteria described in Section 4.2 of this protocol ensure that the patients most at risk with regards to the risks associated with anti-CD19 CAR

T-cell therapy are not included in the study. In addition, all subjects will receive KITE-363 in a hospital setting and will be monitored daily for signs and symptoms of CRS and neurologic events while hospitalized for a minimum of 7 days (refer to Appendix 4). Subjects will also be monitored for the presence of the important potential risks associated with CAR T-cell therapy listed above. In addition, an SRT will be chartered to review the safety data and to make recommendations to the sponsor on study conduct and progression of the study. In summary, as noted in Section 1.1, the treatment of patients with r/r B-cell lymphoma remains challenging and there is a significant unmet need for better therapies in these patients. Because these patients are likely resistant to chemotherapy, they may benefit from therapies with different mechanisms of action. Immunotherapy, which is based on the enhancement of an immune response against the tumor, is a promising approach to treating many cancer types. As noted in Section 1.1.2 and Section 1.5, CAR-engineered T cells have demonstrated impressive results in treating patients with r/r DLBCL. Study KT-US-499-0150 will evaluate the use of KITE-363, a dual-targeting CAR T-cell therapy, in subjects who are refractory or have relapsed with standard of care. The study design is expected to allow for an appropriate assessment of the benefit of KITE-363 in subjects with r/r B-cell lymphomas while maintaining an acceptable safety profile for the risks associated with CAR T-cell therapies. Refer to the current version of the IB for a summary of the findings from nonclinical studies and additional information on the known and potential benefits and risks associated with CAR T-cell therapy.

## Contacts

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**Scientific**
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## Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1) Subjects with any of the following B-cell lymphomas as defined by the WHO 2016 criteria, as determined by the investigator, are eligible for the study as defined below: a) Histologically confirmed r/r LBCL (including all subtypes in WHO 2016 as well as transformed iNHL) and r/r FL Grade 3b with r/r disease after at least 2 lines of systemic therapy that can include auto-SCT. Or subjects with chemorefractory disease to first-line therapy (primary refractory disease) by satisfying any of the following criteria: - Progressive disease (PD) as the best response to first-line therapy - Stable disease (SD) as the best response after at least 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP) with a SD duration of no longer than 6 months from the last dose of therapy - Partial response (PR) as best response after at least 6 cycles of first-line therapy (eg, 6 cycles of R-CHOP) i) Prior therapy must have included an anti-CD20 mAb and an anthracycline-containing chemotherapy regimen. ii) Subjects with transformed iNHL are eligible if r/r after 1 line of therapy to account for prior therapy given before transformation if they received at least 1 line of therapy prior to transformation. b) Histologically confirmed iNHL (including the subtypes below), with r/r disease after at least 2 lines of therapy. SD (without relapse) > 1 year from completion of the last therapy is not eligible. SD (without relapse) < 1 year from completion of therapy is eligible. i) Subtypes include the following: (1) Grade 1, 2, or 3a FL (2) Nodal, extranodal, or splenic MZL ii) Prior therapy must have included an anti-CD20 mAb combined with an alkylating agent c) Histologically confirmed NLPHL with r/r disease after at least 2 lines of systemic chemotherapy d) Histologically confirmed B-cell lymphoma, unclassifiable (with features intermediate between DLBCL and cHL) with r/r disease after at least 2 lines of systemic chemotherapy 2) At least 1 measurable lesion according to the International Working Group (IWG) Lugano Response Criteria for Malignant Lymphoma. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy. If the only measurable disease is lymph-node disease, at least 1 lymph node should be >= 1.5 cm. 3) The following washout periods must be satisfied: a) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis, except for systemic inhibitory/stimulatory immune checkpoint therapy and anti-CD20 mAb therapy. b) At least 3 half-lives must have elapsed after any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time the subject is planned for leukapheresis (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40

agonists, and 4-1BB agonists). c) At least 28 days must have elapsed since any prior anti-CD20 mAb therapy before the KITE-363 infusion. d) At least 4 weeks must have elapsed after any prior immunosuppression therapy before the KITE-363 infusion. Note: This criterion does not apply to subjects who receive bridging Please refer to Table 5 for list of allowed bridging therapy agents. 4) Prior anti-CD19 and anti-CD20 targeted therapies are allowed if administered at least 28 days (if monoclonal antibody) or 3 months (if CAR T-cell product) before the KITE-363 infusion. CD19 and/or CD20 expression must be confirmed, as per local review, after receiving the most recent anti-CD19 or anti-CD20 therapies. If expression is confirmed via biopsy after the most recent anti-CD19/CD20 therapy, this will meet criteria. 5) Toxicities due to immediate prior therapy must be stable and have recovered to Grade 1 or lower. 6) Age 18 or older 7) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 8) Adequate bone marrow function as evidenced by: a) Absolute neutrophil count >= 1,000/µL b) Platelet count >= 75,000/µL unless secondary to bone marrow or spleen involvement by lymphoma where platelet count >= 50,000/ µL. Bone marrow involvement by lymphoma is demonstrated by bone marrow aspiration or biopsy. Spleen involvement by lymphoma is demonstrated by splenomegaly. c) Absolute lymphocyte count >= 100/µL 9) Adequate renal, hepatic, cardiac, and pulmonary function as evidenced by: a) Creatinine clearance (as estimated by any local institutional method) >= 60 mL/minute b) Serum alanine aminotransferase/aspartate aminotransferase <= 2.5 x the upper limits of normal, except in subjects with liver involvement by lymphoma c) Total bilirubin <= 1.5 mg/dL, except in subjects with Gilbert*s Syndrome or documented liver or pancreatic involvement where <= 3.0 times the ULN. d) Cardiac ejection fraction >= 50% and no clinically significant pericardial effusion as determined by an echocardiogram (ECHO) or multiple-gated acquisition scan (if ECHO not available at the site) and no clinically significant electrocardiogram (ECG) findings e) No evidence of Grade 2 or greater pleural effusion or ascites f) Baseline oxygen saturation > 92% on room air 10) Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or have been postmenopausal for at least 2 years before enrollment are not considered to be of childbearing potential)

## Exclusion criteria

1) Grade 4 CRS or Grade 4 neurologic toxicity attributed to prior treatment with a CAR T-cell therapy or other genetically modified T-cell therapy targeting CD19 and/or CD20
2) History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg, cervix, bladder, or breast) unless the subject has been disease free and without anticancer therapy for at least 3 years. Subjects with asymptomatic localized low-grade prostate cancer for which a watch-and-wait approach is standard of care are eligible.
3) History of Richter*s transformation of chronic leukemic lymphoma, small lymphocytic lymphoma, or lymphoplasmacytic lymphoma
4) History of allo-SCT except if no donor cells are detected on chimerism more than 100 days after allo-SCT, the patient is off all immunosuppression, and there is no evidence of active graft-versus-host disease of any grade

5) Auto-SCT within 6 weeks before the planned KITE-363 infusion
6) History of a severe, immediate hypersensitivity reaction attributed to aminoglycosides
7) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requires IV antimicrobials for management. Note: Simple urinary tract infections and uncomplicated bacterial pharyngitis are permitted if the subject is responding to active treatment and the criteria of being afebrile (i.e. temperature < 38°C).
8) Known history of human immunodeficiency virus (HIV) infection, hepatitis B (hepatitis B surface antigen positive) infection, or hepatitis C (anti-hepatitis C virus [HCV] positive) infection. History of a hepatitis B or C infection is permitted if the viral load is undetectable per quantitative polymerase chain reaction (PCR) or nucleic acid testing. Note: Subjects who are seropositive for HBV are eligible if they are HBsAg-negative and negative for viral DNA. Subjects who are seropositive because of HBV vaccination are eligible. Subjects on prophylactic and suppressive antiviral medications against HBV and/or HCV administered per institutional or clinical practice guidelines are eligible.
9) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, G/J-tube or pleural/peritoneal/pericardial catheter). Ommaya reservoirs or other dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted.
10) Subjects with detectable CSF malignant cells or brain metastases or a history of central nervous system (CNS) lymphoma, primary CNS lymphoma, or spinal epidural involvement.
For remaining exclusion criteria, see the Protocol.

# Study design

## Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 16-11-2021 |

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| Enrollment: | 7 |
| Type: | Actual |

### Medical products/devices used

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| Registration: | No |

## Ethics review

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| Approved WMO Date: | 27-06-2022 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 02-03-2023 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 22-03-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 26-05-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 19-07-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 17-11-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den |

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| | Haag) |
| Approved WMO Date: | 20-12-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 12-03-2024 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

# 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 |
|---|---|
| EU-CTR | CTIS2024-511616-24-00 |
| EudraCT | EUCTR2020-000562-41-NL |
| ClinicalTrials.gov | NCT04989803 |
| CCMO | NL81647.000.22 |