4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to approximately 80 subjects will be enrolled in the study, of whom up to approximately 70 subjects will be treated to achieve the following number of subjects in each study phase:

- **Phase 1a:** Up to 30 subjects treated and evaluable for DLT in the dose-escalation cohorts (refer to Section 9.6.1 for a definition of the DLT-evaluable set)
- **Phase 1b:** Up to approximately 40 additional subjects treated in the dose-expansion cohorts

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

To be enrolled in the study, subjects must meet all of the following criteria:

1) Subjects with any of the following B-cell lymphomas as defined by the WHO 2016 criteria {Swerdlow 2016}, 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 {Swerdlow 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 {Cheson 2014}. 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: (see Section 12.4.3 – Germany)

   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 therapy. 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 (except for clinically nonsignificant toxicities such as alopecia)

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 (per Common Terminology Criteria for Adverse Events [CTCAE] 5.0) or greater pleural effusion or ascites (subjects with Grade 1 ascites or pleural effusion are eligible).

   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). Additionally see Section 12.4.2 for UK specific requirements.

4.2.2. Exclusion Criteria

To be enrolled in the study, subjects must not meet any of the following 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 disease free and without anticancer therapy (with the exception of hormonal therapy in the case of breast cancer) 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 satisfies 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 (i.e, Hepatitis B Surface (HBs) and/or hepatitis B core antibody positive) are eligible if they are HBsAg-negative and negative for viral DNA. Subjects who are seropositive because of HBV vaccination are eligible (i.e, HBs antibody-positive, hepatitis core antibody-negative, and HBsAg-negative). 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 (e.g, 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.

11) History or presence of a CNS disorder, such as hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome, or cerebral edema with confirmed structural defects by appropriate imaging. History of stroke or transient ischemic attack within 12 months before enrollment, or seizure disorders requiring active anticonvulsive medication.

12) Subjects with cardiac atrial or ventricular lymphoma involvement

13) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, active arrhythmia, New York Heart Association Class II or greater congestive heart failure or other clinically significant cardiac disease within the 6 months before enrollment

14) Requirement for urgent therapy within 6 weeks before enrollment due to ongoing or impending oncologic emergency (eg, tumor mass effect or tumor lysis syndrome)

15) Primary immunodeficiency

16) History of autoimmune disease (eg, Crohn's, rheumatoid arthritis, or systemic lupus) resulting in or requiring systemic immunosuppression and/or systemic disease-modifying agents within the last 2 years

17) History of concomitant genetic syndrome associated with bone marrow failure such as Fanconi anemia, Kostmann syndrome, or Shwachman-Diamond syndrome.

18) History of non-line associated, clinically significant (CTCAE 5.0 Grade 2 or greater) deep-vein thrombosis (i.e, proximal deep-vein thrombosis) or pulmonary embolism requiring therapeutic anticoagulation within the 3 months before enrollment.

19) Any medical condition likely to interfere with the assessments of safety or efficacy of the study treatment

20) History of a severe hypersensitivity reaction or contraindication to any of the agents used in the study (including fludarabine and cyclophosphamide).

21) Live vaccine ≤ 6 weeks before the planned start date of the lymphodepleting regimen

22) Females of childbearing 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 have been postmenopausal for at least 2 years are not considered to be of childbearing potential

23) Subjects of both genders who are not willing to practice highly effective birth control from the time of informed consent through 6 months after the KITE-363 infusion (Section 12.3)

24) In the investigator's judgment, the subject is unlikely to complete all study-specific visits or procedures, including follow-up visits, or comply with the study requirements for participation

4.3. Subject Withdrawal

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.