4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 247 subjects will be enrolled in the study, of whom approximately 222 subjects will be treated to achieve the following number of subjects in each study phase:

- **Phase 1a:** Up to 42 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). Of these, up to 30 will be treated with KITE-363 and up to 12 will be treated with KITE-753.
- **Phase 1b:** Approximately 100 additional subjects treated in the dose-expansion cohorts. Of these, approximately 40 subjects with r/r LBCL will be treated with KITE-363 and approximately 60 subjects will be treated with KITE-753 consisting of subjects with r/r LBCL in Cohort A and B, frontline LBCL in Cohort C, and r/r MCL in Cohort D.
- **Phase 2**: Approximately 80 subjects with r/r LBCL after at least 2 prior lines of systemic therapy will be treated with KITE-753.

4.2. Eligibility Criteria for Phase 1a/b

4.2.1. Inclusion Criteria for Phase 1a/b

To be enrolled in the Phase 1a/b portion of the study, subjects must meet all of the following criteria:

1) Subjects with any of the following B-cell lymphomas as defined by the fifth edition of the WHO criteria {Alaggio 2022}, as determined by the investigator, are eligible for the study as defined below:

    a) Histologically confirmed r/r LBCL (including all subtypes per the fifth edition of WHO {Alaggio 2022}) as well as TFL, transformed MZL (tMZL), and r/r follicular large B-cell lymphoma (FLBL) after at least 2 prior lines of systemic therapy that can include auto-SCT or subjects with chemorefractory disease to first-line therapy (primary refractory disease) that satisfies any of the following criteria:

        i) PD as the best response to first-line therapy

        ii) Stable disease (SD) as the best response after at least 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP) with an SD duration of no longer than 6 months from the last dose of therapy

        iii) PR as best response after at least 6 cycles of first-line therapy (eg, 6 cycles of R-CHOP)

    b) Prior therapy must have included an anti-CD20 antibody or bispecific T-cell engager antibody with an anthracycline-containing chemotherapy regimen.

c) Subjects with transformed iNHL are eligible if they received at least 1 line of therapy after transformation and meet the definition of r/r disease outlined in criterion 1a above.

d) 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 antibody combined with an alkylating agent

e) Phase 1a only: Histologically confirmed NLPHL with r/r disease after at least 2 lines of systemic chemotherapy

f) Phase 1a only: Histologically confirmed MGZL with r/r disease after at least 2 lines of systemic chemotherapy

g) Phase 1b only: Subjects with frontline LBCL who have SD or PR per Lugano Criteria after 2 or 3 cycles of frontline therapy are eligible. Subjects must have an IPI score of 3 to 5, or if IPI score is < 3, subjects must have HGBCL with *MYC* and *BCL2* rearrangements. Acceptable frontline regimens include, Pola-R-CHP, R-CHOP, or R-EPOCH (may be dose adjusted).

   Note: Subjects with transformed DLBCL from FL or from MZL are eligible if they have not received any prior treatment with an anthracycline-containing regimen

h) Phase 1b only: Histologically confirmed MCL must have documentation of either overexpression of cyclin D1 or presence of t(11;14) per local review

   Note: Subjects with MCL must have received at least 2 prior lines of systemic therapy or 1 prior line of systemic therapy that included a BTKi

   Note: Single-agent anti-CD20 or radiation therapy will not be considered a separate line of therapy for purposes of eligibility for any histology.

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. Splenomegaly or hepatomegaly alone in the absence of a measurable lesion is not considered to be a measurable disease.

3) The following washout periods must be satisfied: (Germany – see Section 12.5.3)

   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 antibody therapy.

      Note: CD20 expression must be confirmed, as per local review, after receiving the most recent anti-CD20 therapies. If expression is confirmed via biopsy after the most recent anti-CD20 therapy, this will meet the criteria.

   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 (if mAb or bispecific T-cell engager antibody) or 90 days (if CAR T cell therapy) must have elapsed after any prior anti-CD19 or anti-CD20 therapy before the KITE-363 or KITE-753 administration.

      Note: 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 the criteria.

   d) At least 4 weeks must have elapsed after any prior immunosuppression therapy before the KITE-363 or KITE-753 administration.

      Note: This criterion does not apply to subjects who receive bridging therapy. Please refer to Table 7 for list of allowed bridging therapy agents.

   e) At least 6 months must have elapsed after any prior bendamustine exposure before leukapheresis

   f) At least 60 days must have elapsed after any prior T-cell engager antibodies before leukapheresis

4) 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, unless otherwise specified in the protocol)

5) Age 18 years or older and who have provided written informed consent

6) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

   Note: For Phase 1b only, subjects with frontline LBCL with an ECOG performance status of ≤ 2 are eligible.

7) 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

8) Adequate renal, hepatic, cardiac, and pulmonary function as evidenced by:

   a) Creatinine clearance (as estimated by any local institutional method) ≥ 55 mL/minute

      Note: 24-hour urine estimate is also acceptable

   b) Serum alanine aminotransferase/aspartate aminotransferase ≤ 3.0 times 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 upper limit of normal

   d) Cardiac ejection fraction ≥ 45% and no pericardial effusion Grade 3 or higher (per CTCAE v5.0) as determined by an echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) (if ECHO not available at the site)

      Note: If there is any concern for pericardial effusion, an ECHO must be performed since MUGA alone is not an adequate modality to assess for pericardial effusion.

   e) No evidence of Grade 2 (per Common Terminology Criteria for Adverse Events [CTCAE] v5.0) or greater pleural effusion or ascites (subjects with Grade 1 ascites or pleural effusion are eligible)

   f) Baseline oxygen saturation > 92% on room air

9) Females of childbearing potential must have a medically supervised 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; refer to Section 12.4). Additionally, see Section 12.5.2 for UK-specific requirements.

4.2.2. Exclusion Criteria for Phase 1a/b

To be enrolled in the Phase 1a/b portion of 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 that is not transformed at the time of screening

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 GVHD of any grade

5) Auto-SCT within 6 weeks before the planned KITE-363 or KITE-753 administration

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 (ie, temperature < 38°C).

8) Known history of HIV infection, hepatitis B virus (HBV) (hepatitis B surface [HBs] antigen [HBsAg] 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 (qPCR) or nucleic acid testing.

   Note: Subjects who are seropositive for HBV (ie, 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 (ie, 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 (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, gastrostomy/jejunostomy 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

    Note: Subjects with controlled atrial fibrillation on a stable regimen are permitted

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 24 months

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 v5.0 Grade 2 or greater) deep-vein thrombosis (ie, proximal deep-vein thrombosis) or pulmonary embolism requiring therapeutic anticoagulation within the 90 days 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 either sex who are not willing to practice highly effective birth control from the time of informed consent through 12 months after the KITE-363 or 12 months after the KITE-753 administration (Section 12.4).

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. Eligibility Criteria for Phase 2

4.3.1. Inclusion Criteria for Phase 2

To be enrolled in the Phase 2 portion of the study, subjects must meet all of the following criteria:

1) Subjects with any of the following B-cell lymphomas as defined by the fifth edition of the WHO criteria {Alaggio 2022}, as determined by the investigator, are eligible for the study as defined below:

    a) Histologically confirmed r/r LBCL (including all subtypes per the fifth edition of the WHO classification unless specified in the exclusion criteria {Alaggio 2022} as well as TFL and tMZL) and r/r FLBL after at least 2 prior lines of systemic therapy that satisfies any of the following criteria:

        i) Prior systemic therapy must include an anti-CD20 antibody or bispecific T-cell engager antibody with an anthracycline-containing chemotherapy regimen

            Note: Single-agent anti-CD20 antibody therapy (such as rituximab or obinutuzumab) does not count as a separate line of systemic therapy

        ii) A line of systemic therapy must include at minimum 1 cycle of the regimen

        iii) Local radiation, single-agent corticosteroids, and maintenance therapies do not constitute as separate lines of systemic therapy

        iv) Auto-SCT counts as 1 line of therapy

2) At least 1 measurable lesion according to the 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. A measurable lesion is defined as ≥ 1.5 cm longest transverse diameter (LDi) for lymph nodes and ≥ 1.0 cm LDi for extranodal lesions. Splenomegaly or hepatomegaly alone in the absence of a measurable lesion is not considered to be measurable disease.

3) The following washout periods must be satisfied:

    a) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed after any prior systemic therapy before leukapheresis, except for T-cell engager antibodies and bendamustine (as indicated below)

    b) At least 60 days must have elapsed after any prior T-cell engager antibodies and before leukapheresis

c) At least 6 months must have elapsed after any prior bendamustine exposure before leukapheresis

4) 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, unless otherwise specified in the protocol)

5) Age 18 years or older and who have provided written informed consent

6) ECOG performance status of ≤ 2

7) Adequate bone marrow function as evidenced by:

a) Absolute neutrophil count ≥ 1,000/μL or ≥ 500/μL if documented bone marrow involvement of lymphoma. Bone marrow involvement by lymphoma is demonstrated by positron emission tomography (PET) scan or bone marrow aspiration or bone marrow biopsy.

b) Platelet count ≥ 75,000/μL (unless secondary to bone marrow or spleen involvement by lymphoma, in which case platelet count ≥ 50,000 μL is permitted). Bone marrow involvement by lymphoma is demonstrated by PET scan or bone marrow aspiration or bone marrow biopsy. Spleen involvement by lymphoma is demonstrated by PET-diagnostic CT involvement, splenomegaly, or biopsy

8) Adequate renal, hepatic, cardiac, and pulmonary function as evidenced by:

a) Creatinine clearance (as estimated by Cockcroft-Gault formula) ≥ 40 mL/minute.

Note: 24-hour urine estimate is also acceptable

b) Serum alanine aminotransferase/aspartate aminotransferase ≤ 3.0 times the upper limit of normal, except in subjects with documented liver involvement by lymphoma via PET-diagnostic CT scan or biopsy

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 upper limit of normal is permitted

d) Cardiac ejection fraction ≥ 45% and no pericardial effusion Grade 3 or higher (per CTCAE v5.0) as determined by an ECHO or MUGA (if ECHO not available at the site)

Note: If there is any concern for pericardial effusion, an ECHO must be performed since MUGA alone is not an adequate modality to assess for pericardial effusion.

e) No evidence of Grade 2 (per CTCAE v5.0) or greater pleural effusion or ascites (subjects with Grade 1 ascites or pleural effusion are eligible)

f) Baseline oxygen saturation > 92% on room air

9) Females of childbearing potential must have a medically supervised 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; refer to Section 12.4). Additionally, see Section 12.5.2 for UK-specific requirements.

4.3.2. Exclusion Criteria for Phase 2

To be enrolled in the Phase 2 portion of the study, subjects must not meet any of the following criteria:

1) Prior CAR therapy or other genetically modified T cell therapy

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) Subjects with the following LBCL WHO 2022 criteria subtypes: Richter's transformation of chronic leukemic lymphoma, small lymphocytic lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, T-cell/histiocyte-rich LBCL, MGZL, plasmablastic lymphoma, intravascular LBCL, primary LBCL of immune privileged sites (including primary CNS lymphoma), fibrin-associated LBCL, fluid overload-associated LBCL, lymphomatoid granulomatosis, and anaplastic lymphoma kinase-positive LBCL

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 GVHD of any grade

5) Auto-SCT within 6 weeks before the planned KITE-753 administration

6) History of a severe, immediate hypersensitivity reaction attributed to aminoglycosides

7) Presence or suspicion 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 for 48 hours (ie, temperature < 38°C)

8) Known history of HBV (HBsAg positive) infection or hepatitis C (anti-HCV positive) infection. History of a hepatitis B or C infection is permitted if the viral load is undetectable per qPCR or nucleic acid testing.

   Note: Subjects who are seropositive for HBV (ie, 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 (ie, 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) HIV-positive, unless taking appropriate anti-HIV medications, having an undetectable viral load by qPCR, and a CD4 count ≥ 200 cells/μL

   Note: HIV-positive subjects in AUS are not permitted regardless of active antiretroviral therapy or undetectable blood viral load

10) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, gastrostomy/jejunostomy tube or pleural/peritoneal/pericardial catheter). Ommaya reservoirs or other dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter and renal stents are permitted

11) Subjects with current, detectable CSF malignant cells or brain metastases, active primary CNS lymphoma involvement, or spinal epidural involvement

12) Presence of the following CNS disorders: hemorrhage, dementia (Grade 2 or higher memory impairment per CTCAE v5.0), 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 6 months before enrollment. Participants with seizure disorders requiring active anticonvulsive medication.

13) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

14) Subjects with full thickness lymphoma involvement of gastric or intestinal lining. Subjects with concern for gastric or intestinal perforation or known contained gastric or intestinal perforation

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

16) Requirement for urgent therapy within 4 weeks before enrollment due to ongoing or impending oncologic emergency (eg, tumor mass effect or tumor lysis syndrome)

17) Primary immunodeficiency

18) History of any medical condition including but not limited to 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 90 days

    Note: At least 90 days or 5 half-lives, whichever is shorter, must have elapsed after any prior immunosuppressive or immunomodulating therapy that impacts T cell function and before leukapheresis

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

20) Any medical condition or residual toxicities from prior therapies per investigator assessment likely to interfere with the assessments of safety or efficacy of the study treatment

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

22) Live vaccine ≤ 6 weeks before the planned start date of the lymphodepleting regimen, during the treatment period, and until immune recovery following the study treatments (refer to Section 12.5 for additional country-specific requirements, as applicable).

23) 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

24) Subjects of either sex who are not willing to practice highly effective birth control from the time of informed consent through 12 months after lymphodepleting chemotherapy or the KITE-753 administration, whichever is longer (refer to Section 12.4)

25) 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

4.4. 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.

Subjects can decline to continue receiving protocol-required treatment and/or other study-specific procedures at any time during the study but continue to participate in certain follow-up elements of the study (Section 7.7). This is referred to as partial withdrawal of consent. Refer to Section 7.7 for instructions on follow-up and data to be collected.

Withdrawal of full consent from the study means that the subject does not wish to receive further protocol-required treatment or undergo study-specific procedures, and the subject does not wish to continue further study follow-up. The investigator is to discuss with the subject the appropriate procedures for withdrawal from the study (refer to Section 7.7).