4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 200 subjects will be enrolled in Part A of the study.

An additional 100 or 200 subjects may be enrolled in Part B of the study based on the adaptive decision (see Section 9) for a total of 200 to 400 subjects.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

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

1) High-risk disease defined as an IPI score of 4 or 5 at initial diagnosis

2) Histologically confirmed LBCL based on 2016 World Health Organization (WHO) classification by local pathology lab assessment, including one of the following:

   a) Diffuse large B-cell lymphoma, NOS

   b) High-grade B-cell lymphoma (HGBL) (including HGBL with MYC and BCL2 and/or BCL6 rearrangements (DHL/THL) based on FISH analysis, and HGBL-NOS)

      Note: Transformed DLBCL from follicular lymphoma or from marginal zone lymphoma is eligible if no prior treatment with anthracycline-containing regimen

3) Ann Arbor Stage III or IV disease

4) Have received only 1 cycle of R-chemotherapy

5) At least 1 measurable lesion per the Lugano Classification {Cheson 2014} on anatomical imaging such as computed tomography (CT) imaging (functional imaging such as PET may not be used to identify a measurable lesion). A measurable lesion is defined as greater than 1.5 cm LDi for lymph node and greater than 1.0 cm LDi for extranodal lesion.

6) Adequate tumor biopsy specimen available for central pathology review (detailed sample collection requirement is in central pathology laboratory manual)

7) Age 18 years or older

8) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 at the time of randomization. Note: ECOG > 2 at diagnosis is acceptable

9) Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function as indicated by:
   a) Absolute neutrophil count (ANC) ≥ 1000/μL
   b) Platelet count ≥ 75,000/μL
   c) Absolute lymphocyte count ≥ 100/μL
   d) Creatinine clearance (as estimated by any local institutional method) ≥ 60 mL/minute
   e) Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels ≤ 2.5 × upper limit of normal (ULN) or ≤ 5 x ULN if documented liver involvement of lymphoma
   f) Total bilirubin ≤ 1.5 mg/dL, except in subjects with Gilbert's Syndrome or documented LBCL liver or pancreatic involvement where ≤ 3.0 x the ULN
   g) Left ventricular ejection fraction (LVEF) ≥ 50% and no evidence of clinically significant pericardial effusion, and no clinically significant abnormal electrocardiogram (ECG) findings
   h) 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)
   i) 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 who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

4.2.2. Exclusion Criteria

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

1) Any prior treatment for LBCL other than the 1 cycle of R-chemotherapy
2) The following WHO 2016 subcategories by local assessment
   a) T-cell/histiocyte-rich LBCL
   b) Primary DLBCL of the CNS
   c) Primary mediastinal (thymic) LBCL
   d) B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
   e) Burkitt lymphoma
   f) History of Richter's transformation of chronic lymphocytic leukemia

3) History of severe immediate hypersensitivity reaction attributed to aminoglycosides

4) Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple bacterial infections are permitted if responding to active treatment. Discussion with the Kite medical monitor is encouraged.

5) History of acute or chronic active hepatitis B or C infection. If there is a positive history of treated hepatitis B or hepatitis C, the viral load must be undetectable per quantitative polymerase chain reaction (PCR) and/or nucleic acid testing

6) Positive for human immunodeficiency virus (HIV) unless taking appropriate anti-HIV medications, with an undetectable viral load by PCR and with a CD4 count > 200 cells/uL

   2) Note: HIV-positive subjects in Australia are not permitted regardless of active anti-retroviral therapy or undetectable blood viral load (Refer to 12.4.4).

7) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, are permitted.

8) Presence of detectable cerebrospinal fluid (CSF)-malignant cells, brain metastases, or a history of central nervous system (CNS) involvement of lymphoma

9) Presence of CNS disorder such as dementia, autoimmune disease with CNS involvement, cerebral edema with confirmed structural defects by appropriate imaging, or seizure disorders requiring active anticonvulsive medication. History of stroke, transient ischemic attack, or posterior reversible encephalopathy syndrome (PRES) within 12 months prior to enrollment.

10) Presence of cardiac atrial or ventricular lymphoma involvement

11) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac disease within 12 months before enrollment

12) Presence of primary immunodeficiency

13) History of <u>any medical condition including but not limited to</u> autoimmune disease (eg, Crohn's disease, rheumatoid arthritis, systemic lupus) requiring maintenance systemic immunosuppression/systemic disease modifying agents within the last 2 years. Endocrine conditions that require maintenance with physiologic dose steroids are allowed.

14) History of non-line associated, clinically significant (CTCAE 5.0 Grade 2 or greater) deep vein thrombosis or pulmonary embolism requiring therapeutic anticoagulation within 6 months of randomization

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

16) History of severe immediate hypersensitivity reaction to any of the agents used in this study, including the lymphodepletion chemotherapy (cyclophosphamide or fludarabine)

17) Receipt of live vaccine ≤ 6 weeks before randomization and/or anticipation of need for such a vaccine during the subject's participation in the study

18) Females of childbearing potential who are pregnant or breastfeeding (due to potentially dangerous effects of the preparative chemotherapy on the fetus or infant)

19) Not willing to practice birth control from the time of consent through at least 12 months after the last dose of axicabtagene ciloleucel or SOCT

20) 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

21) History of malignancy other than non-melanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease free for at least 3 years

22) History of autologous or allogeneic stem cell transplant (SCT)

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.

Subjects can decline to continue receiving protocol-required treatment and/or other study-specific procedures at any time during the study; however, these subjects may still continue to participate in the study and be followed for response evaluation and progression. At a minimum, subjects who discontinue study treatments or procedures, including those who refuse to return for a follow-up visit, should be contacted for safety evaluations and followed for survival; this scenario is referred to as partial withdrawal of consent. Refer to Section 7.6 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. Subject data collected up to withdrawal of consent will be retained and included in the analysis of the study, and, where permitted by local regulations, publicly available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study (refer to Section 7.6).

As part of the study, sites may be asked to conduct searches of public records, such as those establishing survival status, if available and per local guidance, to obtain survival data for any subject for whom the survival status is not known. Sites may also be asked to retrieve autopsy reports, if available, to confirm status of disease at the time of death.