5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

101) Histologically confirmed aggressive B cell NHL, including the following types defined by WHO 2008 (Campo et al, 2011):

- DLBCL not otherwise specified; T cell/histiocyte rich large B cell lymphoma; DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly;

  or

  — primary mediastinal (thymic) large B cell lymphoma

  — transformation of follicular lymphoma to DLBCL will also be included

102) Chemotherapy-refractory disease, defined as one or more of the following:

- No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line therapy chemotherapy are excluded

  — Progressive disease (PD) as best response to first-line therapy

  — Stable disease (SD) as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy

  or

- No response to second or greater lines of therapy

  — PD as best response to most recent therapy regimen

  — SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy

  or

- Refractory post-ASCT

  — Disease progression or relapsed ≤ 12 months of ASCT (must have biopsy proven recurrence in relapsed subjects)

  — if salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy

103) Subjects must have received adequate prior therapy including at a minimum:

a) anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and

b) an anthracycline containing chemotherapy regimen;

c) for subjects with transformed FL must have chemorefractory disease after transformation to DLBCL

104) At least 1 measurable lesion according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson et al, 2007). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy

105) Magnetic resonance imaging (MRI) of the brain showing no evidence of central nervous system (CNS) lymphoma

106) 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. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time the subject is planned for leukapheresis (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc).

107) Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia)

108) Age 18 or older

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

110) Absolute neutrophil count (ANC) ≥ 1000/uL

111) Platelet count ≥ 75,000/uL

112) Absolute lymphocyte count ≥ 100/uL

113) Adequate renal, hepatic, pulmonary and cardiac function defined as:

a) Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min

b) Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 2.5 upper limit of normal (ULN)

c) Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome

d) Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings

e) No clinically significant pleural effusion

f) Baseline oxygen saturation >92% on room air

114) 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)

Additional criteria specific for Phase 2 safety management study **(**Cohorts 3, 4, 5 **and 6)**:

115) Relapsed or refractory large B-cell lymphoma including DLBCL, PMBCL, TFL, and HGBCL after two systemic lines of therapy

5.2. Exclusion Criteria

201) History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years

202) History of Richter's transformation of CLL

203) Autologous stem cell transplant with therapeutic intent within 6 weeks of planned axicabtagene ciloleucel infusion

204) History of allogeneic stem cell transplantation

205) Prior CD19 targeted therapy with the exception of subjects who received axicabtagene ciloleucel in this study and are eligible for re-treatment

206) Prior chimeric antigen receptor therapy or other genetically modified T cell therapy

207) History of severe, immediate hypersensitivity reaction attributed to aminoglycosides

208) Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management.

209) History of human immunodeficiency virus (HIV) infection or acute or chronic active hepatitis B or C infection. Subjects with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America (IDSA) guidelines or applicable country guidelines.

210) Presence of any indwelling line or drain (e.g., 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

211) Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma or primary CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases

212) History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement

213) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

214) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment

215) Expected or possible requirement for urgent therapy within 6 weeks due to ongoing or impending oncologic emergency (eg, tumor mass effect, tumor lysis syndrome)

216) Primary immunodeficiency

217) History of symptomatic deep vein thrombosis or pulmonary embolism **requiring systemic anticoagulation** within 6 months of enrollment

218) Any medical condition likely to interfere with assessment of safety or efficacy of study treatment

219) History of severe immediate hypersensitivity reaction to any of the agents used in this study

220) Live vaccine ≤ 6 weeks prior to planned start of conditioning regimen

221) 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

222) Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of conditioning chemotherapy

223) 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

224) History of autoimmune disease (e.g. Crohn's, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years