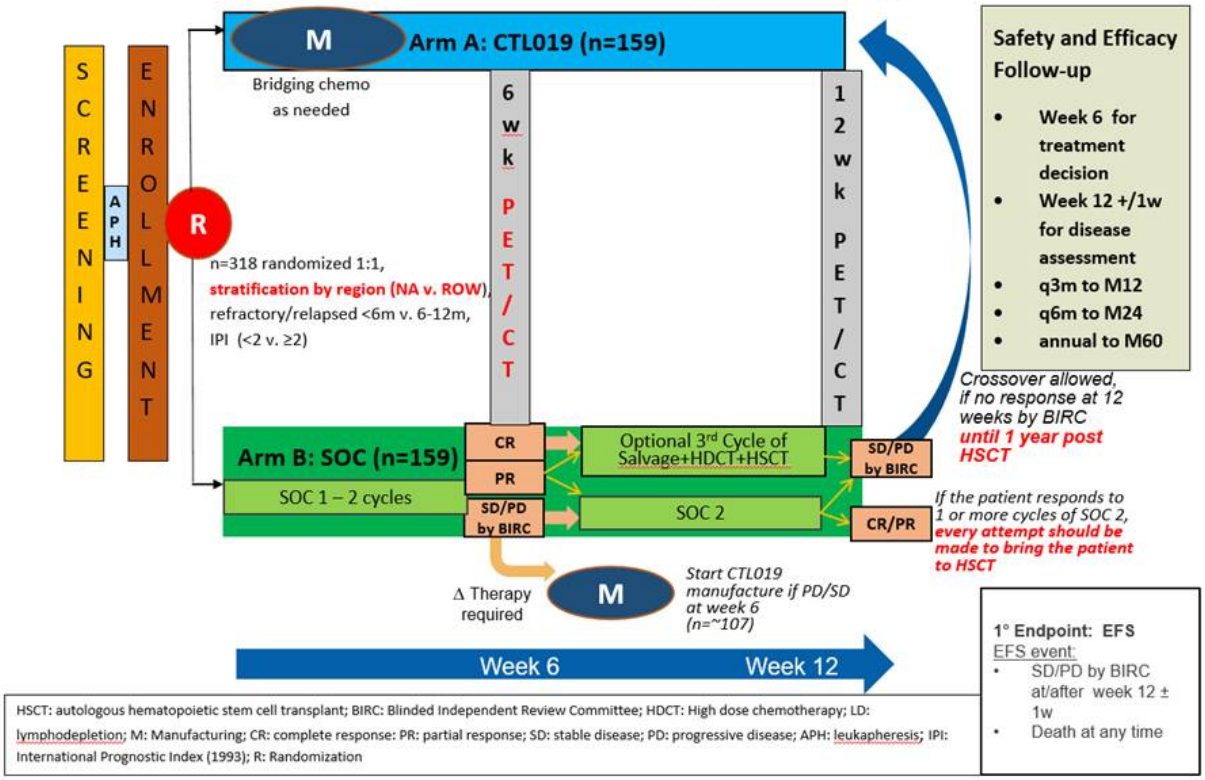
CCTL019H2301 Study Design



HSCT: autologous hematopoietic stem cell transplant; BIRC: Blinded Independent Review Committee; HDCT: High dose chemotherapy; LD: lymphodepletion; M: Manufacturing; CR: complete response: PR: partial response; SD: stable disease; PD: progressive disease; APH: leukapheresis; IPI: International Prognostic Index (1993); R: Randomization

NOVARTIS

CHECKLIST FOR VERIFICATION OF INCLUSION & EXCLUSION CRITERIA

Protocol Identification:	**CCTL019H2301 (BELINDA)**	**Patient No.:**	2500-XXX
Site Number:	2500	**Patient Initials:**	

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are randomized in the study.

No.	Inclusion Criterion	Checked?	Comment (if applicable)
1.	**Signed informed consent must be obtained prior to participation in the study.**	☐	
2.	**Patients must be ≥ 18 years of age at the time of informed consent form (ICF) signature.**	☐	
3.	**Histologically confirmed (by local histopathological assessment), aggressive B-cell NHL at relapse/progression after front line therapy. If biopsy after relapse/progression is not available or it is not clinically feasible to obtain a new biopsy, an archival tumor biopsy from the initial diagnosis may be submitted instead (Refer to Protocol Section 8.5.3) Aggressive B-cell NHL is heretofore defined by the following list of subtypes (circle one):** • **DLBCL, NOS** • **FL grade 3B,** • **Primary mediastinal B cell lymphoma (PMBCL),** • **T cell rich/histiocyte rich large B cell lymphoma (T/HRBCL),** • **DLBCL associated with chronic inflammation,** • **Intravascular large B-cell lymphoma,** • **ALK+ large B-cell lymphoma,** • **B-cell lymphoma, unclassifiable, (with features intermediate between DLBCL and classical HL),** • **High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements,** • **High grade B-cell lymphoma, NOS** • **HHV8+ DLBCL, NOS** • **DLBCL transforming from follicular lymphoma** • **DLBCL transforming from marginal zone lymphoma** • **DLBCL, leg type**	☐	
4.	**Relapse or progression within 365 days from last dose of rituximab and anthracycline containing first line immunochemotherapy or refractory (have not achieved a CR or PR).**	☐	

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5.	**Patient is considered eligible for Autologous HSCT as per local investigator assessment. Note: Intention to transplant and type of HDCT regimen will be documented in the IRT system**	☐	
6.	**Measurable disease:** • **Nodal lesions > 15 mm in the long axis, regardless of the length of the short axis, and/or** • **Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) > 10 mm in long AND short axis**	☐	
7.	**ECOG performance status 0 or 1**	☐	
8.	**Adequate organ function:** **a. Renal function defined as:** • **Serum creatinine of ≤1.5 x ULN, OR eGFR ≥ 60 mL/min/1.73 m2** **b. Hepatic function defined as:** • **ALT and AST ≤ 5 × ULN** • **Total Bilirubin ≤ 1.5 × ULN with the exception of patients with Gilbert syndrome who may be included if their total bilirubin is ≤ 3.0 × ULN and direct bilirubin ≤ 1.5 × ULN** **c. Hematologic Function (regardless of transfusion) defined as:** • **Absolute neutrophil count (ANC) > 1000/mm^3** • **Absolute lymphocyte count (ALC) > 300/mm^3** • **Absolute number of CD3+ T cells > 150/mm^3** • **Platelets ≥ 50,000/mm^3** • **Hemoglobin > 8.0 g/dl** **d. Adequate pulmonary function defined as:** • **No or mild dyspnea (≤ Grade 1)** • **Oxygen saturation measured by pulse oximetry > 90% on room air** • **Forced expiratory volume in 1 s (FEV1) ≥ 50% or carbon monoxide diffusion test (DLCO) ≥ 50% of predicted level**	☐ ☐ ☐ ☐	
9.	**Must have a leukapheresis material of non-mobilized cells available for manufacturing. (Refer to Protocol Section 8.1 and the Leukapheresis, Cryopreservation, and Scheduling manual for details on leukaphresis collection requirements)**	☐	

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1.	Epstein Barr Virus positive (EBV+) DLBCL, NOS, Richter's transformation, and Burkitt lymphoma, and primary DLBCL of CNS	☐	
2.	Prior treatment with anti-CD19 therapy, adoptive T cell therapy, or any prior gene therapy product	☐	
3.	Treatment with any lymphoma-directed second line anticancer therapy prior to randomization. Only steroids are permitted for disease control	☐	
4.	Active CNS involvement by disease under study are excluded, except if the CNS involvement has been effectively treated (i.e. patient is asymptomatic) and local treatment was > 4 weeks before randomization	☐	
5.	Prior allogeneic HSCT	☐	
6.	Investigational medicinal product (IMP) within the last 30 days prior to screening Note: IMPs should not be used at any time while on study until the first progression following tisagenlecleucel infusion	☐	
7.	Presence of active hepatitis B or hepatitis C (see Section 16.1 Appendix 1 of the protocol).	☐	
8.	HIV positive patients	☐	
9.	Clinically significant active infection confirmed by clinical evidence, imaging, or positive laboratory tests (e.g., blood cultures, PCR for DNA/RNA, etc.)	☐	
10.	Any of the following cardiovascular conditions: a. Unstable angina, myocardial infarction, coronary artery bypass graft (CABG), or stroke within 6 months prior to screening, b. LVEF < 45% as determined by ECHO or MRA or MUGA at screening	☐	

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No.	Exclusion Criterion	Checked?	Comment (if applicable)
	c. NYHA functional class III or IV, at screening or within the past 12 months. **d. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II) and third degree AV block, unless adequately controlled by pacemaker implantation.** **e. Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) at screening or inability to determine the QTcF interval** **f. Risk factors for Torsades de Pointes (TdP), including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/ symptomatic bradycardia, or any of the following:** **i. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome** **ii. Concomitant medication(s) with a "Known Risk of Torsades de Point" per www.qtdrugs.org that cannot be discontinued or replaced by safe alternative medication**		
11.	**Previous or concurrent malignancy except for curatively treated non-melanoma skin cancers, in situ carcinoma (e.g. cervix, breast, bladder, prostate), and cancers in complete remission for at least 3 years and without evidence of recurrence**	☐	
12.	**Hypersensitivity to the excipients of tisagenlecleucel or to any other drug product as advised for administration in the study protocol (e.g. lymphodepleting agents, tocilizumab)**	☐	
13.	**Active neurological autoimmune or inflammatory disorders (e.g., Guillain-Barré Syndrome (GBS), Amyotrophic Lateral Sclerosis (ALS)) and clinically significant active cerebrovascular disorders (e.g., cerebral edema, posterior reversible encephalopathy syndrome (PRES))**	☐	
14.	**Pregnant or nursing (lactating) women** **Note: Women of child-bearing potential must have a negative serum pregnancy test performed within 24 hours before leukapeheresis.**	☐	

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No.	Exclusion Criterion	Checked?	Comment (if applicable)
15.	**Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception starting from the time of informed consent form (ICF) signature and for:** • **at least 12 months after the tisagenlecleucel infusion and until CAR T cells are no longer present by qPCR on two consecutive tests for patients in Arm A or patients who crossover.** • **a duration according to local label and physician recommendations for patients randomized to Arm B (SOC). Furthermore, patients may need to also add barrier contraception methods if required by the local label.** **Highly effective contraception methods include:** • **Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception** • **Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment** • **Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject** • **Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.** **In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.** **Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate**	☐	

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No.	Exclusion Criterion	Checked?	Comment (if applicable)
	history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. **Note: If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.** **In addition, participants must not donate oocytes.**		
16.	**Sexually active males who do not use a condom during intercourse while starting from the time of ICF signature and for:** • **at least 12 months after the tisagenlecleucel infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests for patients in Arm A or patients who crossover.** • **a duration according to local label and physician recommendations for patients randomized to Arm B (SOC)** **A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner.** **In addition, participants must not donate sperm**	☐	
17.	**Patients who, in the investigator's judgment and/or according to clinical standards, have a contradiction to any study procedure or have any other medical condition that may put the patient at unacceptable risk.**	☐	

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RANDOMIZATION VISIT: **Herewith I confirm that I checked the inclusion and exclusion criteria as specified above and I verified the criteria assessable at today's visit against the source documents of the patient.**				
The patient is eligible for study participation at this visit:			**YES** ☐	**NO** ☐
Checklist completed by (name and role):		**Date of completion:**		
Signature:				