Miltenyi Biomedicine GmbH CONFIDENTIAL 01. Sep. 2021
Protocol M-2020-371
Inclusion & Exclusion Criteria, based on protocol Version 3.0_NL

Inclusion Criteria
Participants are **eligible** to be included in this study **only if all of the following criteria apply**:

1. Histologically proven DLBCL and associated subtypes, according to the WHO 2016 classification including:

- DLBCL not otherwise specified (NOS).
- High-grade B-cell lymphoma (HGBL) with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double hit lymphoma/triple hit lymphoma).
- High-grade BCL, NOS.
- Primary (thymic) large mediastinal BCL.
- Disease transformed from an earlier diagnosis of low-grade lymphoma (e.g. an indolent pathology such as follicular lymphoma, marginal zone lymphoma) into DLBCL with DLBCL disease progression subsequent to DLBCL directed systemic treatment.

2. Relapsed or refractory disease after first-line chemoimmunotherapy:

- Refractory disease is defined as no CR to first-line therapy,
- PD as best response after at least 4 full cycles of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone) cycles as first-line therapy.
- Stable disease (SD) after 6 R-CHOP cycles as first-line therapy.
- PR as best response after at least 6 R-CHOP cycles and biopsy-proven disease progression (except where prohibited due to comorbidities) within ≤ 12 months from the completion of the first-line therapy.
- Relapsed disease defined as complete remission to a first-line therapy followed by biopsy-proven disease progression (except where prohibited due to comorbidities) within ≤ 12 months from the completion of the first-line therapy.

3. Participant must have received adequate first-line therapy containing at least the combination of an anthracycline-based regimen and rituximab (anti-CD20 monoclonal antibody). Local therapies (e.g. radiotherapies) will not be considered as line of therapy if performed during the same line of treatment.

4. Archival paraffin-embedded tumour tissue acquired ≤ 3 years prior to screening for central pathology review to confirm DLBCL diagnosis and for analysis of CD20/CD19 expression must be made available for participation in this study. If archival paraffin-embedded tumour tissue is not available, fresh tumour tissue sample (preferred) or core-needle biopsy for this protocol must be made available.

5. Participants deemed ineligible to receive HDC followed by ASCT based on the treating physician's assessment and meeting the following criteria:

- Age ≥ 18 years and
  - Prior ASCT (as first-line consolidation) or
  - Haematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) > 3.
- Age ≥ 65 years and 1 of the criteria below:
  - Prior ASCT (as first-line consolidation), or
  - Comorbidities as assessed by an HCT-CI score > 3, or
  - Impaired cardiac function (left ventricular ejection fraction (LVEF) < 50%), or
  - Impaired renal function (creatinine clearance [CrCl] < 60 mL/min) as determined by MDRD (Modification of Diet in Renal Disease) formula or
  - Impaired pulmonary function (diffusing capacity for carbon monoxide or forced expiratory volume in 1 second of 66% to 80%) or dyspnoea on slight activity, or

- Eastern Cooperative Oncology Group (ECOG) performance status > 1.

Documentation of the reason for ineligibility for ASCT must be present in the participant's source data.

In addition, all participants must fulfil the following criteria:
6. Age ≥18 years.

7. Measurable disease according to Lugano criteria. The lesion must be positive on a positron emission tomography scan.

8. Estimated life expectancy of > 3 months for other reasons than the primary disease.

9. Woman of childbearing potential (WOCBP) must agree to use highly effective contraceptive measures (Pearl index < 1) or practice true sexual abstinence from any heterosexual intercourse (True abstinence is only acceptable if it is in line with the preferred and usual life style of the participant.) or must have a vasectomised partner as the sole sexual partner (The vasectomised partner must have received medical assessment of the surgical success.) for at least 1 month before the study start, during the study and in the 12 months following the last dose of study treatment. A woman is considered a WOCBP, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Highly effective methods of contraception include hormonal contraceptives (oral, intravaginal, transdermal, injectable, implantable) and intrauterine devices or systems (e.g. hormonal and non-hormonal) and bilateral tubal occlusion. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. WOBC must refrain from egg donation throughout the study until 12 months after the last dose of study treatment.

Men must agree to use 2 acceptable methods for contraception (e.g. spermicide and condom) or practice true sexual abstinence from any heterosexual intercourse (True abstinence is only acceptable if it is in line with the preferred and usual life style of the participant.), unless they are surgically sterile (meaning at least 2 consecutive analyses following vasectomy demonstrate absence of sperms in the ejaculate), during the study and in the 12 months following the last dose of study treatment. Men must furthermore refrain from sperm donation throughout the study until 12 months after the last administration of study treatment.

10. In the opinion of the investigator, the participant must be able to comply with all study-related procedures, medication use and evaluations.

11. Mental capacity and legal ability to consent to participation in the clinical study.

Exclusion Criteria
Participants are **not eligible** to be included in this study **if any of the following criteria apply**:

1. Contraindications for R-GemOx and BR plus polatuzumab vedotin as judged by the treating physician.

2. Prior chimeric antigen receptor therapy or other genetically modified T-cell therapy.

3. ECOG performance status > 2.

4. Absolute neutrophil count < 1,000/µL (unless secondary to bone marrow involvement by DLBCL as demonstrated by bone marrow biopsy required for screening).

5. Platelet count < 50,000/µL (unless secondary to bone marrow involvement by DLBCL as demonstrated by bone marrow biopsy required for screening).

6. Absolute lymphocyte count < 100/µL.

7. Participants who have CNS lymphoma involvement in present or past medical history.

8. Known history of infection with human immunodeficiency virus or active infection with hepatitis B (hepatitis B surface antigen positive).

9. Known history of infection with hepatitis C virus unless treated and confirmed to be polymerase chain reaction negative.

10. Active infection with SARS-CoV-2.

11. Known history or evidence of severely immunocompromised state; i.e. corticosteroid treatment > 10 mg/day for more than 6 months.

12. Has received vaccination with live virus vaccines within 6 weeks prior to randomisation.

13. Prior CD19 targeted therapy

14. Known history or presence of seizure activities or on active antiseizure medications within the previous 12 months.

15. Presence of CNS disease that, in the judgement of the investigator, may impair the ability to evaluate neurotoxicity.

16. Known history or presence of autoimmune CNS disease, such as multiple sclerosis, optic neuritis or other immunologic or inflammatory disease.

17. Known history or presence of cerebral vascular accident (CVA) within 12 months prior to randomisation.

Note: In case of history of CVA > 12 months prior to leukapheresis, then the participant must not have any unstable or life-threatening neurological deficits.
18. Participants with Richter's transformation or Richter's syndrome.

19. Participants who are concurrently on any other experimental treatments or during the previous 4 weeks or 5-half-lives.

20. Clinical heart failure with New York Heart Association class ≥ 2 or LVEF < 30%.

21. Resting peripheral oxygen saturation < 90% on room air.

22. Liver dysfunction as indicated by total bilirubin, aspartate aminotransferase and/or alanine aminotransferase > 5 × institutional upper limit of normal (ULN).

23. Serum creatinine ≥ 2.0 × ULN or CrCl < 30 mL/min calculated according to the modified formula of MDRD.

24. Pregnant or breast-feeding woman.

25. Prior history of malignancies other than DLBCL, unless the participant has been free of the disease for ≥ 3 years prior to screening. Exceptions to the ≥ 3-year time limit include history of the following:

- Basal cell carcinoma of the skin.
- Squamous cell carcinoma of the skin.
- Carcinoma in situ of the cervix.
- Carcinoma in situ of the breast.
- Carcinoma in situ of the bladder.
- Incidental histological finding of untreated localized (T1a or T1b) prostate cancer under surveillance.

26. History of severe immediate hypersensitivity reaction against any drug or its ingredients/impurities that is scheduled to be given during study participation e.g. as part of the mandatory lymphodepletion protocol, premedication for infusion, or rescue medication/salvage therapies for treatment-related toxicities.

27. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment.

28. Refusal to participate in CAR T long-term follow-up (LTFU).