

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/blastoid/intermediate histology or HGBL with MYC and BCL2 and/or BCL6 rearrangements (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 (e.g. R-CHOP).
 - Progressive disease (PD) as best response after at least 2 full cycles of first-line therapy.
 - Stable disease (SD) after 4 cycles of first-line therapy.
 - PR as best response after at least 6 cycles of first-line therapy and biopsy-proven persistent disease (except where prohibited due to comorbidities) within ≤ 12 months from the completion of the first-line therapy.
 - Relapsed disease defined as complete remission to 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 ≤ 2 years (preferred: ≤ 2 months) prior to screening for the central pathology review to confirm DLBCL diagnosis 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 must be made available for the central pathology review.

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

EITHER

- Age \geq 18 years and
- Prior ASCT (as first-line consolidation) or
- Haematopoietic cell transplantation-specific comorbidity index (HCT-CI) $>$ 3.

OR

- Age \geq 65 years and one of the criteria below:
- Impaired cardiac function (left ventricular ejection fraction [LVEF] $<$ 50%), or
- Impaired renal function (estimated glomerular filtration rate [eGFR] $<$ 60 mL/min) calculated according to the modified Modification of Diet in Renal Disease (MDRD) formula, or
- Impaired pulmonary function (diffusing capacity for carbon monoxide or forced expiratory volume in 1 second $<$ 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 \geq 18 years.

7. Measurable disease according to Lugano criteria. The lesion must be measurable ($>$ 1.5 cm in the long axis) and 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 associated with inhibition of ovulation (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. WOCBP who want to become pregnant after completing treatment should seek advice about oocyte cryoconservation prior to treatment because of possible irreversible infertility. WOCBP must refrain from egg donation throughout the study until 12 months after the last dose of study treatment.

Men with non-pregnant WOCBP partners must agree to use highly effective contraceptive measures (Pearl index $<$ 1, e.g. spermicide and condom or other highly effective contraceptive measures (Pearl index $<$ 1) taken by their WOCBP partner) 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 should seek advice about sperm conservation prior to treatment because of possible irreversible infertility. Men must furthermore refrain from sperm donation throughout the study until 12 months after the last administration of study treatment.

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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, BR plus polatuzumab vedotin, cyclophosphamide and fludarabine as judged by the treating physician.

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

3. Participants who have received more than one line of prior therapy for DLBCL or associated subtypes.

4. Prior HSCT (as first-line consolidation) < 3 months at the time of leukapheresis.

5. ECOG performance status > 2.

6. Absolute neutrophil count < 1,000/ μ L (unless secondary to bone marrow involvement by DLBCL as demonstrated by bone marrow biopsy).

7. Platelet count < 50,000/ μ L (unless secondary to bone marrow involvement by DLBCL as demonstrated by bone marrow biopsy).

8. Absolute lymphocyte count < 100/ μ L.

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

10. Participants with the requirement for urgent therapy due to tumor mass effects.

11. Infection with human immunodeficiency virus.

12. Presence of active or prior hepatitis B or C as indicated by serology (for detailed criteria see Section 10.2.7.10). Treated infection with hepatitis B or C virus unless confirmed to be polymerase chain reaction negative.

13. Active infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

14. Active, severe systemic fungal, viral or bacterial infection.

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

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

17. Prior CD19-targeted therapy.

18. Known history or presence of seizure activities or on active anti-seizure medications within the previous 12 months.

19. History or presence of non-malignant CNS disease that, in the judgement of the investigator, may impair the ability to evaluate neurotoxicity.

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

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21. 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.

22. Participants with Richter's transformation or Richter's syndrome.

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

24. Clinical heart failure with New York Heart Association class ≥ 2 or LVEF < 30% or severe cardiac arrhythmias or QT prolongation (resting QTcF ≥ 450 msec [male] or ≥ 460 msec [female] at screening) that would (according to the evaluation of the investigator) face an uncontrollable risk by receiving the medications administered in the trial.

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

26. Liver dysfunction as indicated by total bilirubin > 2.5 \times institutional upper limit of normal (ULN), aspartate aminotransferase and/or alanine aminotransferase > 5 \times ULN or typical symptoms like jaundice.

27. Serum creatinine $\geq 2.0 \times$ ULN or eGFR < 30 mL/min calculated according to the modified MDRD formula.

28. Pregnant or breastfeeding woman.

29. Prior history of malignancies other than DLBCL. Exceptions include participants who have been free of the disease for ≥ 3 years prior to screening and participants with adequately treated and removed 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 or incidental histological finding of untreated localised (T1a or T1b) prostate cancer under surveillance.

30. History of severe immediate hypersensitivity to any investigational medicinal product (IMP), auxiliary medicinal product (AMP), premedication or rescue medication or its excipients that is scheduled to be given during study participation.

31. Major surgery less than 30 days before start of treatment.

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