BRENTUXIMAB VEDOTIN IN COMBINATION WITH LENALIDOMIDE AND RITUXIMAB IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (ECHELON-3, TRIAL IN PROGRESS)

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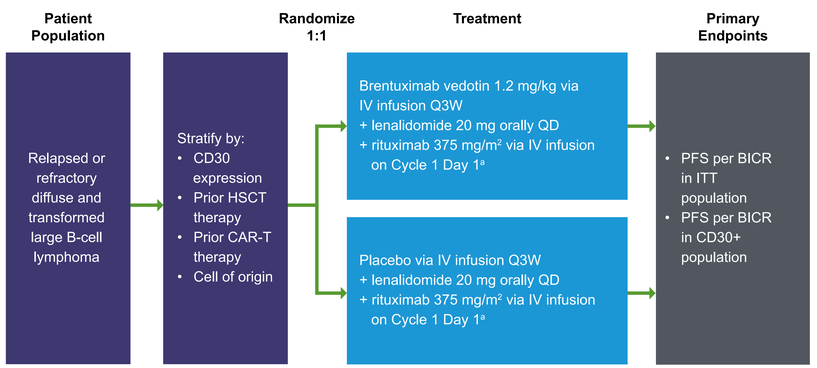
Background and Rationale

- The majority of patients with R/R DLBCL who relapse after HSCT or CAR-T therapy, or who are not candidates for HSCT or CAR-T therapy, have poor outcomes and are in need of novel therapies.[1]
- BV (ADCETRIS®) was the first antibody–drug conjugate to be approved in multiple cancer types.[2]
- The unique combination of a CD30-directed monoclonal antibody, the protease-cleavable linker, and the microtubule-disrupting agent MMAE drives the anticancer activity of BV.[3]
  - MMAE-mediated microtubule disruption induces cell cycle arrest and apoptosis.[3]
  - Direct cytotoxicity is at the heart of the multifaceted anticancer activity of BV, including the induction of immunogenic cell death, which promotes activation and recruitment of immune cells to tumors.[3–9]
- Lenalidomide may enhance the activity of BV through immune-mediated mechanisms.
- In a phase 1 trial (NCT02086604) of 37 patients with R/R DLBCL who received BV + lenalidomide (manuscript in press *Blood*):
  - The ORR was 56.7% in all patients, and 73.3% in CD30-expressing patients.
  - The median duration of remission was 13.2 months in patients with a CR or PR, and 11.7 months in patients with a CR, PR, or SD >6 months.
  - The median PFS and median OS were 10.2 months and 14.3 months, respectively, and results were similar in the CD30-expressing and CD30 <1% groups.
- The proven clinical activity and manageable safety profile of each agent, and differing but complementary mechanisms of action, provides a strong rationale for evaluating the combination of rituximab, lenalidomide, and BV in heavily pre-treated patients with R/R DLBCL.

Study Design

- ECHELON-3 (NCT04404283) is a randomized, double-blind, placebo-controlled, active-comparator, multicenter, phase 3 study designed to evaluate the efficacy of BV versus placebo, in combination with lenalidomide and rituximab, in patients with R/R DLBCL.
- A run-in period assessing the safety and pharmacokinetic profile of BV, lenalidomide, and rituximab for the first cycle of treatment in 6 patients has been completed, and the Safety Monitoring Committee agreed the study should proceed to the randomized phase.
- Patients (n=400) will be randomized 1:1 to receive either BV or placebo in combination with lenalidomide and rituximab, and will be stratified by:
  - CD30 expression (≥1% [positive] versus <1% [negative]); at least 200 CD30-expressing patients will be enrolled
  - Prior allogeneic or autologous HSCT (received or not)
  - Prior CAR-T-cell therapy (received or not)
  - Cell of origin (GCB or non-GCB)
- Patients will receive primary granulocyte-colony stimulating factor prophylaxis.
- If dose reduction is required due to adverse events, BV can be reduced to 0.9 mg/kg every 3 weeks, and lenalidomide can be reduced in 5-mg increments to a minimum dose of 5 mg daily.
- Treatment may continue as long as there is clinical benefit (SD or better) without progression or unacceptable toxicity.

Figure 1: ECHELON-3 Study Design



[a]Rituximab 1400 mg via subcutaneous injection is permitted Q3W from Cycle 2 Day 1 through to end of treatment.

Eligibility Criteria

Table 1: Key Inclusion Criteria

- Patients aged ≥18 with R/R DLBCL of an eligible subtype:
  - NOS
  - DLBCL arising from transformed indolent lymphomas/leukemias
  - High-grade B-cell lymphoma with translocations of *MYC* and *BCL2* and/or *BCL6* (double-/triple-hit lymphoma)
  - High-grade NOS B-cell lymphomas
  - Primary mediastinal large B-cell lymphoma
  - T-cell-/histiocyte-rich large B-cell lymphoma
  - Epstein-Barr virus positive NOS
  - Primary cutaneous DLBCL (leg type)
  - Intravascular large B-cell lymphoma
  - DLBCL associated with chronic inflammation
  - Anaplastic lymphoma kinase positive
- R/R disease following ≥2 prior lines of systemic therapy, and ineligible for or unable to receive HSCT or CAR-T therapy
- Fluorodeoxyglucose-avid disease by PET and bidimensional measurable disease of at least 1.5 cm by CT
- ECOG performance status of 0 to 2
- The following baseline laboratory data within 28 days prior to Day 1:
  - ANC ≥1000/μL
  - Platelet count ≥50,000/μL
  - Serum bilirubin ≤1.5 x ULN or ≤3 x ULN for patients with Gilbert's disease or documented hepatic involvement with lymphoma
  - eGFR ≥60 mL/min/1.73 m²
  - ALT and AST ≤3.0 x ULN or ≤5.0 x ULN for patients with documented hepatic involvement with lymphoma

Table 2: Key Exclusion Criteria

- History of another malignancy within 2 years before the first dose of study drug or any evidence of residual disease from a previously diagnosed malignancy
- History of progressive multifocal leukoencephalopathy
- Active cerebral/meningeal disease related to the underlying malignancy
- Any uncontrolled Grade ≥3 (per NCI CTCAE version 5.0[10]) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study drug
- Grade ≥2 peripheral sensory or motor neuropathy at baseline
- Current use of immunosuppressive medications; low dose steroids are permitted
- Previous exposure to BV or lenalidomide

Study Assessments

- Disease response will be assessed by BICR and the investigator according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas.[11]
- Radiographic disease evaluations, including contrast-enhanced CT and PET, will be assessed at baseline, every 6 weeks from randomization until Week 48, and then every 12 weeks.
- PET will not be required after CR is achieved.
- Tumor biopsy obtained <4 weeks prior to enrollment will be assessed for CD30 expression by immunohistochemistry determined by central lab. Use of a local pathology lab to determine CD30 expression may be allowed after discussion with the medical monitor.

Endpoints

Primary

- PFS assessed by BICR in the ITT population
- PFS assessed by BICR in the CD30-expressing population

Secondary

- OS in the ITT population
- OS in the CD30-expressing population
- ORR as assessed by BICR in the ITT population
- CR rate
- Duration of objective response
- Safety and tolerability (per NCI CTCAE version 5.0[10])

Exploratory

- Association of CD30 expression with ORR and PFS
- ORR and PFS based on Response Evaluation Criteria in Lymphoma[12]
- BV serum concentrations and incidence of antidrug antibody to BV
- Association of molecular biomarkers with ORR and PFS
- Patient-reported outcome assessments based on EuroQol-5 dimension-5 level, National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Lymphoma, and healthcare utilization

Statistical Analyses

- The stratified log-rank test will be used to compare time-to-event efficacy endpoints, including PFS and OS, between the 2 treatment groups.
- Time-to-event endpoints will be summarized using the Kaplan-Meier method, and HRs will be estimated using the stratified Cox regression model.

Summary

- BV in combination with rituximab and lenalidomide is a promising treatment combination for patients with R/R DLBCL who are ineligible for or unable to receive HSCT or CAR-T therapy.
- The ECHELON-3 trial will assess the efficacy and safety of this combination in R/R DLBCL patients, stratified by CD30 expression, cell of origin, and prior HSCT or CAR-T therapy.
- Enrollment for this global trial is currently ongoing or planned in the following countries: Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Italy, the Netherlands, Poland, Republic of Korea, Spain, Switzerland, Taiwan, the UK, and the USA.

Abbreviations

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BCL, B-cell lymphoma; BICR, blinded independent central review; BV, brentuximab vedotin; CAR-T, chimeric antigen receptor T-cell; CR; complete response; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; GCB, germinal center B cell; HR, hazard ratio; HSCT, hematopoietic stem cell transplant; ITT, intent-to-treat; IV, intravenous; MMAE, monomethyl auristatin E; NCI, National Cancer Institute; NOS, not otherwise specified; ORR, objective response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; QD, once daily; R/R, relapsed/refractory; SD, stable disease; ULN, upper limit of normal.

References

1. Crump M, et al. (2017). Blood 130:1800-08.
2. Gauzy-Lazo L, et al. (2020). SLAS Discov 25(8):843-68.
3. Sutherland MS, et al. (2006). J Biol Chem 281(15):10540-7.
4. Li F, et al. (2016). Cancer Res 76(9):2710-9.
5. Gardai SJ, et al. (2016). Haematologica 101(S5):53.
6. Müller P, et al. (2014). Cancer Immunol Res 2(8):741-55.
7. Oflazoglu E, et al. (2007). Blood 110(13):4370-2.
8. Heiser RA, et al. (2018). Cancer Res 78(13 Suppl):Abstract nr 1789.
9. Herrera AF, et al. (2018). Blood 131(11):1183-94.
10. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0 (November 27, 2017). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Accessed October 2021.
11. Cheson BD, et al. (2014). J Clin Oncol 32:3059-68.
12. Younes A, et al. (2017). Ann Oncol 28:1436-47.

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