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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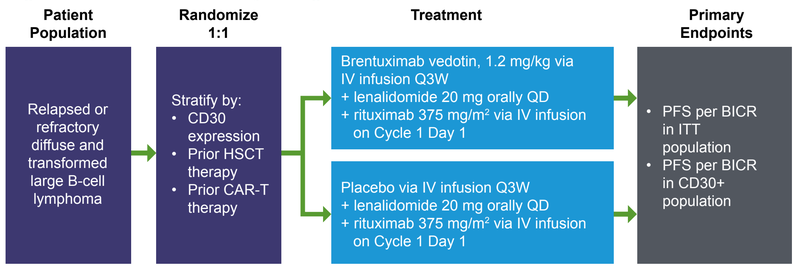
Background and Rationale

- The majority of patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who relapse after hematopoietic stem cell transplantation (HSCT) or chimeric antigen receptor T-cell (CAR-T) therapy, or who are not candidates for HSCT or CAR-T, have poor outcomes and are in need of novel therapies[1]
- Brentuximab vedotin (BV) is an antibody–drug conjugate composed of a monoclonal antibody, a protease-cleavable linker, and the cytotoxic payload monomethyl auristatin E (MMAE)[2]
- The primary mechanism of action (MoA) of BV is through directing the tubulin-disrupting agent MMAE to CD30-expressing cells.[3] In addition, BV-mediated cytotoxicity may be augmented by immune cell stimulation and bystander effects[4,5]
- In a phase 1 trial of 37 patients with R/R DLBCL who received BV + lenalidomide, the objective response rate (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 complete response (CR) or partial response (PR) and 11.7 months in patients with CR, PR, or stable disease (SD) for over 6 months
  - The median progression-free survival (PFS) and median overall survival (OS) were 10.2 months and 14.3 months, respectively, and results were similar in the CD30-expressing and CD30 <1% groups (manuscript submitted)
- The proven clinical activity, unique MoA, and manageable safety profile of each agent provides a strong rationale for evaluating the combination of rituximab, lenalidomide, and BV in 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 + 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 + rituximab, and will be stratified by:
  - CD30 expression (≥1% versus <1% [negative]); at least 200 CD30-expressing patients will be enrolled
  - Prior allogeneic or autologous stem cell transplant (received or not)
  - Prior CAR-T-cell therapy (received or not)
  - Cell of origin (germinal center B-cell [GCB] or non-GCB)
- Patients will receive primary granulocyte-colony stimulating factor prophylaxis
- Rituximab 1400 mg via subcutaneous injection is permitted every 3 weeks from Cycle 2 Day 1 through to the end of treatment
- 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



BICR, blinded independent central review; CAR-T, chimeric antigen receptor T-cell; HSCT, hematopoietic stem cell transplant; ITT, intent-to-treat; IV, intravenous; PFS, progression-free survival; Q3W, every 3 weeks; QD, once daily.

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 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 0 to 2

The following baseline laboratory data within 28 days of 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 m^2
- ALT and AST ≤3.0 x ULN or 5.0 x ULN for patients with documented hepatic involvement with lymphoma

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CAR-T, chimeric antigen receptor T-cell; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; HSCT, hematopoietic stem cell transplant; NOS, not otherwise specified; PET, positron emission tomography; R/R, relapsed/refractory; ULN, upper limit of normal.

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) 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

CTCAE, Common Terminology Criteria for Adverse Events; HSCT, hematopoietic stem cell transplant; NCI, National Cancer Institute.

Study Assessments

- Disease response will be assessed by blinded independent central review (BICR) and the investigator according to the Lugano Classification Revised Staging System
- Radiographic disease evaluations, including contrast-enhanced computed tomography and positron emission tomography (PET), will be assessed at baseline, every 6 weeks from randomization until Week 48, and then every 12 weeks
- PET is not required after CR is achieved
- Tumor biopsy obtained <4 weeks prior to enrollment with 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
  - ≥1% CD30 tumor expression will be considered CD30-expressing
  - <1% CD30 tumor expression will be considered CD30-negative

Endpoints

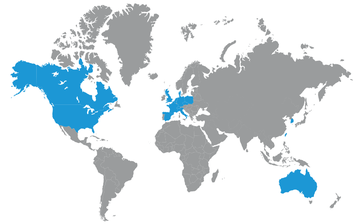
Primary
- PFS assessed by BICR in the intent-to-treat (ITT) population
- PFS assessed by BICR in the CD30-expressing population

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 National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0)

Exploratory
- Association of CD30 expression with ORR and PFS
- ORR and PFS based on Response Evaluation Criteria in Lymphoma 2017
- BV serum concentrations and incidence of antidrug antibody to BV
- Association of molecular biomarkers with ORR and PFS
- EuroQol-5 dimension-5 level, National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Lymphoma, and healthcare utilization

Summary

- BV in combination with rituximab and lenalidomide is a promising treatment combination for patients with R/R DLBCL who are 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 in the following countries: Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Italy, the Netherlands, Poland, Republic of Korea, Spain, Switzerland, Taiwan, UK, and the USA



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