ABCL-313

waveLINE-011: Zilovertamab Vedotin Plus Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (R-CHP) Versus Polatuzumab Vedotin Plus R-CHP as First-Line Therapy in Germinal Center B-Cell–Like Diffuse Large B-Cell Lymphoma

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Presented by Melissa Drysdale on behalf of the authors

Background

- Diffuse large B-cell lymphoma (DLBCL) is categorized into 3 subgroups based on gene expression profiling: germinal center B-cell–like (GCB), activated B-cell–like, and unclassified DLBCL[1]
- Standard of care for first-line treatment of DLBCL is polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)[2]
- Polatuzumab vedotin plus R-CHP showed significant improvement in progression-free survival (PFS) compared with R-CHOP as first-line treatment for DLBCL in all participants, with a trend toward better outcomes in high-risk subgroups; however, for participants with the GCB subtype, PFS was similar for polatuzumab vedotin plus R-CHP compared with R-CHOP[3]
- Novel therapies with higher response rates, durable remission, and manageable safety profiles are needed for first-line treatment of DLBCL, including the GCB subtype
- Zilovertamab vedotin is a novel antibody-drug conjugate targeting the tumor-specific receptor tyrosine kinase–like orphan receptor 1 (ROR1) and delivering a cytotoxic payload, monomethyl auristatin E[4]
- Zilovertamab vedotin in combination with R-CHP has shown promising efficacy and manageable safety as first-line treatment in participants with DLBCL, including the GCB subtype, in a phase 2 study[5]
- The randomized, open-label, phase 2 waveLINE-011 study (NCT06890884) is ongoing and will evaluate the efficacy and safety of zilovertamab vedotin plus R-CHP versus polatuzumab vedotin plus R-CHP in participants with previously untreated GCB subtype of DLBCL

Objectives

Primary

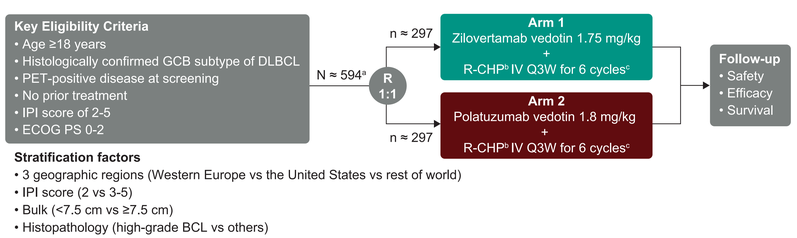
- To evaluate the complete response (CR) rate at end of treatment (EOT) per Lugano response criteria as assessed by blinded independent central review (BICR) of zilovertamab vedotin plus R-CHP versus polatuzumab vedotin plus R-CHP

Secondary

- To evaluate the following in participants treated with zilovertamab vedotin plus R-CHP versus polatuzumab vedotin plus R-CHP
  - PFS per Lugano response criteria by BICR (key secondary)
  - Overall survival (OS)
  - Event-free survival (EFS)
  - Duration of CR per Lugano response criteria by BICR
  - Safety and tolerability
  - Changes from baseline in health-related quality-of-life assessments

Methods

Study design



Stratification factors
- 3 geographic regions (Western Europe vs the United States vs rest of world)
- IPI score (2 vs 3-5)
- Bulk (<7.5 cm vs ≥7.5 cm)
- Histopathology (high-grade BCL vs others)

BCL, B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; IV, intravenous; PET, positron emission tomography; Q3W, every 3 weeks; R, randomization.

[a]The actual number of participants randomly assigned per local cell-of-origin testing may be adjusted to ensure the random assignment of 504 participants with the GCB subtype confirmed by central cell-of-origin testing.

[b]Rituximab 375 mg/m^2 plus cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and prednisone 100 mg/day. Prednisone will be administered by mouth on days 1 and 5 of each 3-week cycle.

[c]Participants with high-risk DLBCL with an IPI score of 3-5 will receive 2 additional cycles of rituximab or biosimilar.

Participant eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Histologically confirmed GCB subtype of DLBCL, according to WHO classification of neoplasms of hematopoietic and lymphoid tissue, including but not limited to – DLBCL, NOS, GCB type – High-grade BCL, GCB subtype • *MYC*, *BCL2*, and/or *BCL6* rearrangement • With 11q aberration • High-grade BCL, NOS • PET-positive disease at screening (4 or 5 on the Lugano 5-point scale) • No prior treatment for DLBCL • IPI score of 2-5[a] • ECOG PS score of 0-2[b] • Adequate organ function	• History of transformation of indolent disease to DLBCL • Diagnosis of primary mediastinal BCL or gray zone lymphoma • Ann Arbor stage I DLBCL • Clinically significant (active) cardiovascular disease • Clinically significant pericardial or pleural effusion • Ongoing grade >1 peripheral neuropathy • A demyelinating form of Charcot-Marie-Tooth disease • HIV and history of Kaposi sarcoma and/or multicentric Castleman disease • Ongoing corticosteroid therapy (exceeding 30 mg/day of prednisone equivalent) • Known additional malignancy that is progressing or has required active treatment within the past 2 years • Known active central nervous system lymphoma • Active autoimmune disease that has required systemic treatment in the past 2 years • Active infection requiring systemic therapy • Concurrent active hepatitis B or C virus infection • History of allogeneic tissue/solid organ transplant

NOS, not otherwise specified; WHO, World Health Organization.
[a]Participants with an IPI score of 2 will be capped at 40% per arm.
[b]Participants with an ECOG PS score of 2 will be capped at 20% per arm.

Assessments and follow-up

Assessment	Detail
Response	• Response assessments (CT/FDG-PET) will be performed after day 1 of cycle 4 but on or before day 1 of cycle 5, and then at 12 weeks after cycle 4 scan (EOT assessment) • Follow-up assessments will be completed every 24 weeks for 2 years from EOT assessment, then every year for 3 years (total of 5 years)
AEs	• AEs will be monitored and assessed by investigators throughout the study and for 30 days after the last dose of study treatment (90 days, or 30 days if new anticancer therapy is initiated, for serious AEs) • AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0
PROs	• PRO measures will be administered before dosing on day 1 of every cycle, at the EOT visit, and at the 30-day safety follow-up visit

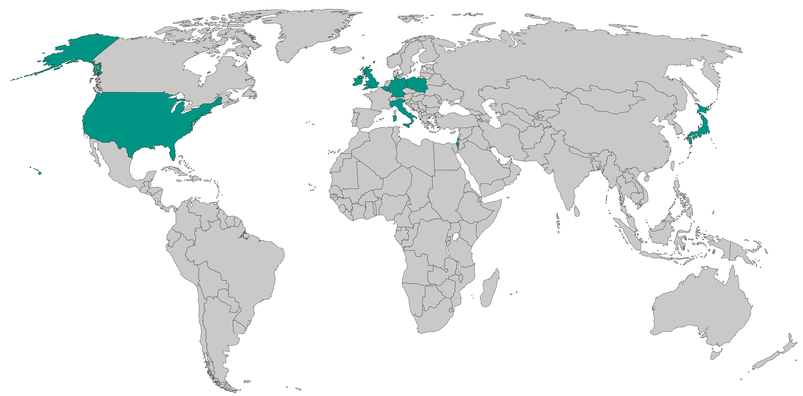
AE, adverse event; CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; PRO, patient-reported outcome.

Analyses

Analysis	Detail
Efficacy	• Efficacy will be assessed in the full analysis set population, defined as all randomly assigned participants with GCB subtype confirmed by central test • CR rate at EOT (primary end point) will be compared between treatment groups using the stratified Miettinen-Nurminen method with strata weighting by sample size, and point estimates and 95% CIs will be calculated using the exact binomial method • PFS (key secondary end point) will be compared between treatment groups by a stratified log-rank test; hazard ratio and 95% CI will be estimated using a stratified Cox proportional hazards model using the Efron method of tie handling. The nonparametric Kaplan-Meier method will be used to estimate the survival curve in each treatment group • Duration of CR will be summarized using Kaplan-Meier medians and quartiles (if sample size permits)
Safety	• Safety analyses will be conducted in the all-participants-as-treated population, defined as all participants who receive ≥1 dose of study treatment • Safety will be described descriptively
PROs	• PROs will be assessed in all randomly assigned participants who have ≥1 PRO assessment and have received ≥1 dose of study treatment

Status

Sites of participant enrollment for waveLINE-011 (green)



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