ABCL-579

# Zilovertamab Vedotin Alone or in Combination With Nemtabrutinib in Relapsed or Refractory Aggressive and Indolent B-Cell Malignancies (waveLINE-006): An Open-Label Phase 2 Basket Study

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## Background

- Treatment options are needed after first-line therapy for patients with hematologic malignant neoplasms[1]
- Receptor tyrosine kinase–like orphan receptor 1 (ROR1) is a transmembrane protein expressed in hematologic malignant neoplasms[2]
  - Zilovertamab vedotin is an antibody-drug conjugate composed of humanized immunoglobulin G1 (IgG1) monoclonal anti-ROR1, a proteolytically cleavable linker, and the antimicrotubule agent monomethyl auristatin E (MMAE); it has shown promising antitumor activity in hematologic malignant neoplasms[2]
- Bruton tyrosine kinase (BTK) is a key downstream regulator of the B-cell receptor signal transduction pathway; activation of this pathway regulates B-cell physiology, including differentiation, proliferation, adhesion, cell migration, and survival[3]
  - Nemtabrutinib is an oral, reversible, noncovalent competitive inhibitor of wild-type and *C481S*-mutant BTK that provides promising antitumor activity in multiple B-cell malignant neoplasms[4,5]
- The combination of zilovertamab vedotin and a BTK inhibitor could potentially improve responses in patients with B-cell malignant neoplasms[6]
- The waveLINE-006 (NCT05458297) multicenter, open-label, phase 2 study is designed to investigate the safety and efficacy of zilovertamab vedotin as monotherapy or in combination with nemtabrutinib in patients with relapsed or refractory (R/R) B-cell malignant neoplasms, including mantle cell lymphoma (MCL; cohorts A and C), Richter transformation (RT; cohort B), or follicular lymphoma (FL; cohorts D and E)

## Objectives

### Primary

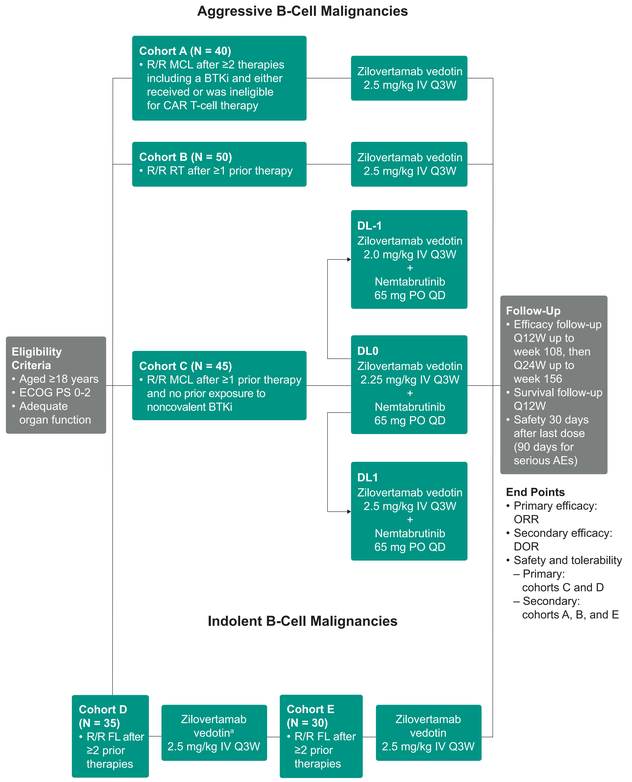
- To evaluate safety and tolerability of zilovertamab vedotin in patients with FL (cohort D) or zilovertamab vedotin plus nemtabrutinib in patients with MCL (cohort C)
- To evaluate objective response rate (ORR) for
  - Zilovertamab vedotin for patients with MCL (cohort A), RT (cohort B), and FL (cohorts D and E) per Lugano response criteria[7] by blinded independent central review (BICR)
  - Zilovertamab vedotin plus nemtabrutinib for patients with MCL (cohort C) per Lugano response criteria by investigator review

### Secondary

- To evaluate safety and tolerability of zilovertamab vedotin in patients with MCL (cohort A), RT (cohort B), or FL (cohort E)
- To evaluate duration of response (DOR) for
  - Zilovertamab vedotin for patients with MCL (cohort A), RT (cohort B), or FL (cohorts D and E) per Lugano response criteria by BICR
  - Zilovertamab vedotin plus nemtabrutinib for patients with MCL (cohort C) per Lugano response criteria by investigator review

## Methods

### Study design




AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; DL, dose level; IV, intravenous; PO, by mouth; Q3W, every 3 weeks; Q2/3W, every 2 or 3 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks; QD, once daily; R, randomization; RP2D, recommended phase 2 dose.

[a]A previous version of the protocol enrolled CLL patients at this dose level and CLL and FL patients at 2.0 mg/kg IV Q2/3W.

### Patient eligibility

| Cohort | Key inclusion criteria | Key exclusion criteria |
|---|---|---|
| All | • Aged ≥18 years<br>• ECOG PS 0-2<br>• Adequate organ function | • Prior ROR1-directed therapy[a]<br>• Active CVD<br>• Acute or chronic GVHD in patients with prior allo-SCT<br>• Systemic anticancer therapy ≤4 weeks before first study dose (≤2 weeks for small molecules)<br>• Prior radiotherapy ≤28 days before first study dose<br>• Ongoing corticosteroid therapy >30 mg QD of prednisone equivalent<br>• Current or prior participation in a study of an investigational agent or device ≤4 weeks before first study dose<br>• Solid organ transplant recipient<br>• Ongoing grade ≥1 peripheral neuropathy<br>• FL transformation into more aggressive lymphoma<br>• Active HBV/HCV infection, active infection necessitating systemic therapy, active CNS disease, history of HIV<br>• Cohort C only<br>– QTc prolongation (QTcF >450 ms) or other ECG abnormalities<br>– Current treatment with CYP2C8 substrates, P-gp substrates, CYP3A strong inducers<br>– Any GI abnormalities that might alter absorption |
| A | • Histologically confirmed MCL<br>• Measurable disease per Lugano response criteria assessed by the investigator and verified by BICR<br>• R/R disease after ≥2 prior systemic therapies, including a BTKi<br>• Previous CAR T-cell therapy or ineligible for CAR T-cell therapy | |
| B | • Histologically confirmed RT<br>• Measurable disease per Lugano response criteria assessed by the investigator and verified by BICR<br>• R/R disease after ≥1 prior systemic therapy | |
| C | • Histologically confirmed MCL<br>• Measurable disease per Lugano response criteria assessed by the investigator<br>• R/R disease after ≥1 prior systemic therapy<br>• No prior exposure to a noncovalent BTKi | |
| D | • Histologically confirmed grade 1-3A FL<br>• Measurable disease per Lugano response criteria assessed by the investigator and verified by BICR, and clinical features that mandate treatment<br>• R/R disease after ≥2 prior systemic therapies and no other available therapy | |
| E | • Histologically confirmed grade 1-3A FL<br>• Measurable disease per Lugano response criteria assessed by the investigator and verified by BICR, and clinical features that mandate treatment<br>• R/R disease after ≥2 prior systemic therapies and no other available therapy | |

allo-SCT, allogeneic stem cell transplant; CNS, central nervous system; CVD, cardiovascular disease; CYP, cytochrome P450; ECG, electrocardiography; GI, gastrointestinal; GVHD, graft-versus-host disease; HBV, hepatitis B virus; HCV, hepatitis C virus; QTc, corrected QT interval; QTcF, corrected QT interval by Fridericia; P-gp, P-glycoprotein.

[a]Prior exposure to MMAE-containing drugs is allowed.

### Assessment and follow-up

| Assessment | Detail |
|---|---|
| Tumor response | • Assessed by CT or PET Q12W from C1D1 up to week 108, then Q24W up to week 156<br>• Follow-up tumor imaging to be performed at discontinuation |
| AEs | • AEs will be monitored throughout the study by the investigator and for 30 days (90 days for serious AEs) after the last dose of study drug; they will be graded per the NCI CTCAE v5.0 |
| DLTs | • Dose finding will follow the mTPI design (cohort C) with a target DLT rate of 27%<br>• The initial DLT period will be the first 56 days (safety run-in phase) for cohort C; thereafter, DLTs will be evaluated every 6 months |

C1D1, cycle 1 day 1; CT, computed tomography; DLT, dose-limiting toxicity; mTPI, modified toxicity probability interval; NCI CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; PET, positron emission tomography.

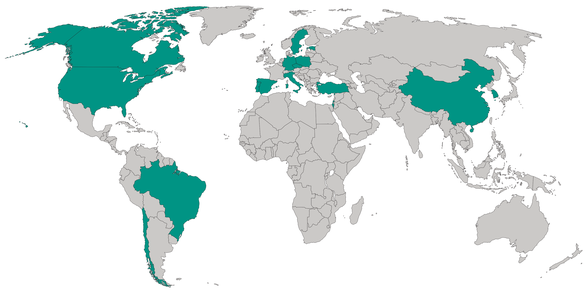
### Analyses

| Analysis | Detail |
|---|---|
| Efficacy | • Efficacy analyses will be conducted in the APaT population, defined as all patients who received ≥1 dose of study drug<br>• Analyses will be pooled by disease type and dosing schedule<br>• ORR and 95% CIs will be estimated using the Clopper-Pearson exact binomial method<br>• DOR will be estimated using the Kaplan-Meier method |
| Safety | • Safety analyses will be conducted in the APaT population<br>• Analyses will be pooled by disease type and dosing schedule<br>• Safety and tolerability will be summarized using descriptive statistics<br>• DLT rate across doses will be estimated using the pool-adjacent violators algorithm |

APaT, all patients as treated.

## Status

### Sites of patient enrollment for waveLINE-006 (green)



### References

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### Acknowledgments

The authors thank the patients and their families and caregivers for participating in this trial and all investigators and site personnel. Medical writing and/or editorial assistance was provided by Bresler Swanepoel, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Presented at the Society of Hematologic Oncology (SOHO) 2024 Annual Meeting; Houston, Texas; September 4-7, 2024

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