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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Bellwave-010: Phase 3, Open-Label, Randomized Study of Nemtabrutinib Plus Venetoclax Versus Venetoclax Plus Rituximab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Following at Least One Prior Therapy

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Background: Venetoclax + rituximab (VR) is a standard therapy among patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who have relapsed after at least 1 line of prior therapy. However, there is an unmet need for more effective treatments. Bruton's tyrosine kinase (BTK) is a critical signaling molecule in the pathogenesis of CLL, and inhibitors of BTK have resulted in significant improvements in survival for patients with CLL. Nemtabrutinib is a noncovalent, reversible, competitive inhibitor of BTK that does not require the C481 residue of BTK for binding and inhibition of kinase activity. As a result, nemtabrutinib can target both wild-type and C481-mutant forms of BTK. Results from the ongoing BELLWAVE-001 study have demonstrated manageable safety and durable antitumor activity of nemtabrutinib in patients with CLL/SLL with and without C481 mutations. The randomized, active-controlled, open-label, phase 3 BELLWAVE-010 study (NCT05947851) is designed to investigate the efficacy and safety of nemtabrutinib + venetoclax versus VR as second-line (2L) or later treatment for patients with relapsed/refractory (R/R) CLL/SLL.
Study Design and Methods: Patients aged ≥18 years with active CLL/SLL that is relapsed/refractory to at least 1 prior therapy per the iwCLL 2018 criteria, an ECOG performance status of 0-2, and adequate organ function are eligible. Patients with Richter transformation, active central nervous system involvement, or severe bleeding disorder are excluded. Approximately 720 patients will be enrolled in 2 parts: an open-label, nonrandomized dose escalation and confirmation phase (part 1) to evaluate safety and determine the optimal dose of nemtabrutinib in combination with venetoclax and an open-label, parallel-group, randomized phase (part 2) comparing the efficacy and safety of nemtabrutinib + venetoclax with VR. In part 1, 30 patients will be enrolled to establish the dose of nemtabrutinib using a modified toxicity probability interval design. Patients will receive nemtabrutinib at 2 dose levels (45 mg PO QD starting dose, escalating to 65 mg PO QD) for 28 days followed by the combination of nemtabrutinib + venetoclax (20-400 mg PO QD ramp up over 4 weeks). In part 2, approximately 690 patients will be randomly assigned 1:1 to receive either nemtabrutinib at the recommended dose for 28 days followed by the combination of nemtabrutinib + venetoclax (20-400 mg PO QD ramp up over 4 weeks) or venetoclax (20-400 mg PO QD ramp up over 4 weeks) + rituximab (or rituximab biosimilar; 375 mg/m ^{2} at week 6 followed by 500 mg/m ^{2} Q4W starting at week 10 until week 26 [total 6 doses]). Patients will receive study treatment for ~2 years or until unacceptable toxicity, disease progression, or other discontinuation criteria are met. Randomization will be stratified by BTK-C481 mutation status (detected vs not detected; determined by droplet digital PCR with a limit of detection of approximately 0.01%-0.1%), geographic region (US/Canada vs Europe vs rest of world) and risk (high risk [del(17p) and/or *TP53*-mutated and/or *IGHV*-unmutated] vs low risk [absence of high-risk factors]). Response will be assessed (including imaging, physical examination, constitutional symptoms, hematological evaluations, and bone marrow biopsy as required) every 12 weeks up to week 97 and every 24 weeks thereafter or more frequently if clinically indicated. Adverse events will be monitored up to 30 days after treatment cessation (90 days for serious adverse events) and will be graded per NCI CTCAE, version 5.0. Hematologic toxicities will be evaluated according to iwCLL 2018 criteria. Patient-reported outcomes will be assessed using the EORTC QLQ-C30, EORTC QLQ-CLL17, and EQ-5D-5L questionnaires. The primary end points for part 1 are safety and tolerability, including dose-limiting toxicities, and to establish the recommended dose of nemtabrutinib in combination with venetoclax. The primary end point for part 2 is PFS as assessed per iwCLL 2018 criteria by blinded independent central review (BICR). Secondary end points for part

2 include undetectable minimal residual disease in bone marrow at month 14 as assessed by central laboratory, ORR, and DOR per iwCLL 2018 criteria by BICR, OS, and safety. Exploratory end points include ORR including partial response with lymphocytosis, pharmacokinetics, and health-related quality of life.

Disclosures Lavie: *Medisson:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Takeda:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Lecture; *Roche:* Honoraria, Other: Advisory Board; *AbbVie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Advisory Board and Travel/Accommodation expenses; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Lecture; *MSD:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel/Accommodation expenses, lecture. **Ozcan:** *Acerta:* Research Funding; *MSD:* Research Funding; *Pfizer:* Research Funding; *Takeda:* Research Funding; *Roche:* Research Funding; *PSI:* Research Funding; *Janssen:* Research Funding; *Bayer:* Research Funding; *Abbvie:* Other: Travel/Accommodations/Expenses, Research Funding; *Sandoz:* Other: Travel/Accommodations/Expenses. **Chaudhry:** *AON:* Current Employment; *Novartis:* Current holder of *stock options* in a privately-held company; *AstraZeneca, Beigene, Arcus, Amgen, Merck, Lilly/Loxo:* Research Funding. **Zhou:** *Merck & Co., Inc.:* Current Employment, Current equity holder in publicly-traded company. **Paydar:** *Merck & Co., Inc.:* Current Employment, Current equity holder in publicly-traded company. **Farooqui:** *Merck & Co., Inc.:* Current Employment, Current equity holder in publicly-traded company. **Ghia:** *Lilly/Loxo Oncology:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria, Research Funding; *BMS:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *BeiGene:* Consultancy, Honoraria, Research Funding; *MSD:* Consultancy, Honoraria, Research Funding; *Roche:* Consultancy, Honoraria, Research Funding.

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