P682 NEMTABRUTINIB (MK-1026), A NON-COVALENT INHIBITOR OF WILD-TYPE AND C481S MUTATED BRUTON TYROSINE KINASE FOR B-CELL MALIGNANCIES: EFFICACY AND SAFETY OF THE PHASE 2 DOSE-EXPANSION BELLWAVE-001 STUDY

**Topic:** 06. Chronic lymphocytic leukemia and related disorders - Clinical


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**Background:** For patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and certain B-cell neoplasms, resistance to Bruton tyrosine kinase inhibitors (BTKi) develops primarily through mutations at the cysteine binding site (C481) or PLCγ2 mutations. Nematbrutinib (MK-1026, formerly ARQ-531) is a non-covalent, potent inhibitor of both wild type and C481-mutated BTK.

**Aims:** In the phase 1/2 dose-escalation and dose-expansion BELLWAVE-001 study (NCT03162536), the preliminary recommended dose 2 (RP2D) of nemtabrutinib was determined to be 65 mg once daily. The efficacy and safety of nemtabrutinib in patients (pts) with CLL/SLL and B-cell non-Hodgkin lymphoma (NHL) were also evaluated at a higher dose during the dose-expansion phase.

**Methods:** In this open-label, single-arm phase 2 study, 9 expansion cohorts were initiated following determination of preliminary nemtabrutinib RP2D. Approximately 10-25 eligible pts were enrolled into Cohort A (relapsed/refractory (r/r) CLL/SLL, with ≥2 prior therapies including covalent BTKi, with documented C481 mutation), Cohort B (r/r CLL/SLL progressed on/intolerant to a BTKi, with ≥2 prior therapies without C481 mutation), Cohort C (Richter transformation with ≥1 prior therapy), Cohort D-H (follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, high-grade B cell lymphoma with known MYC, BCL-2 or BCL-6 translocations, and Waldenström macroglobulinemia [WM], respectively, who received ≥2 prior therapies), Cohort I (food-effect cohort including pts with B-cell NHL, CLL/SLL, and WM). Primary end point was ORR (per iwCLL criteria, by investigator) for participants with CLL/SLL. Secondary end points included DOR and safety and tolerability.

**Results:** Among 118 pts enrolled, 44 had B-cell NHL, 68 CLL/SLL, and 4 WM. Of these, 94 (79.6%) were treated at the preliminary RP2D, including 51 (54.3%) participants with CLL/SLL. Pts with CLL/SLL had a median (range) number of prior therapies of 4 (1-18), 43 (84%) had prior BTKi therapy, 12 (23%) had del17p, 30 (59%) had IGHV unmutated status, and 32 (63%) had C481S BTK mutation. At data cut-off (April 7, 2021), median (range) follow-up was 4.6 mo (0.1-26.7) for all treated pts. ORR was 57.9% (22/38; 1 CR, 21 PR/PRL) per iwCLL criteria in the efficacy-evaluable population of pts with CLL/SLL treated at preliminary RP2D. Median duration of response was not estimable [NE] (range, 8.3 mo-NE). Among all treated participants, 114 (97%) had a treatment-emergent adverse event (TEAE), with 78 (66%) having a drug-related TEAE, and 9 (8%) having a drug-related TEAE that led to discontinuation. Common TEAEs (≥ 20%) included fatigue (33%), constipation (31%), dysgeusia (28%), cough (25%), nausea (25%), pyrexia (25%), dizziness (23%), hypertension (23%), peripheral edema (22%), diarrhea (21%), and arthralgia (20%). Grade ≥3 TEAEs occurred in 80 (68%) participants. Grade 5 TEAEs occurred in 7 (6%) participants.
participants and included death following disease progression 3 (3%), sepsis 1 (1%), dyspnea 1 (1%), and respiratory failure 2 (2%). Common drug-related TEAEs (≥10%) included dysgeusia (15%), nausea (11%), fatigue (11%), and decreased neutrophil count (10%). Grade 3-4 drug-related TEAEs occurred in 31 (26%) participants. No drug-related TEAEs led to death.

**Summary/Conclusion:** Nemtabrutinib has promising antitumor activity with a manageable safety profile in pts with CLL/SLL exposed to multiple lines of therapy, including in those who had progression of disease on prior covalent BTKi. Further evaluation of nemtabrutinib in B-cell malignancies is ongoing.