Preliminary Efficacy and Safety of MK-1026, a Non-Covalent Inhibitor of Wild-Type and C481S Mutated Bruton Tyrosine Kinase, in B-Cell Malignancies: A Phase 2 Dose Expansion Study

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Introduction:

Bruton tyrosine kinase inhibitors (BTKi) have revolutionized the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and certain B-cell neoplasms. However, resistance to BTKi develops primarily through mutations at the cysteine binding site (C481) or PLCγ2 mutations. MK-1026 (formerly ARQ-531) is a non-covalent, potent inhibitor of both wild type and C481- mutated BTK. In the phase 1/2 dose escalation and dose expansion study NCT03162536, the preliminary recommended phase 2 dose (RP2D) of MK-1026 was determined to be 65 mg once daily. The efficacy and safety of MK-1026 in participants 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 MK-1026 RP2D. Approximately 10-25 eligible participants 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 (participants with Richter transformation [RT] with ≥1 prior therapy), Cohort D-H (participants with follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), high-grade B cell lymphoma (BCL) 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 participants with B-cell NHL, CLL/SLL, and WM). Treatment continued until unacceptable toxicity, clinical or radiological progression, participant/physician withdrawal. Primary endpoint was overall response rate (per iwCLL criteria, by investigator) for participants with CLL/SLL. Secondary endpoints included duration of response and safety and tolerability. The data cut-off date for this analysis was April 7, 2021.

Results:

Among 118 participants enrolled, 44 had B-cell NHL (including 6 with DLBCL,

11 with FL, 3 with high-grade BCL, 6 with MCL, 2 with MZL, 16 with RT), 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. Participants 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, 26 (51%) had IGHV unmutated status, and 32 (63%) had C481S BTK mutation. At data cut-off, median (range) follow-up was 4.56 months (0.1-26.7) for all treated participants. ORR was 57.9% (N = 22 of 38; 1 CR, 21 PR/PRL) per iwCLL criteria in the efficacy evaluable population of participants with CLL/SLL treated at preliminary RP2D. The median duration of response in these participants was not estimable [NE] (range, 8.3 months-NE). At data cut-off, the median duration of treatment exposure was 3.2 months (range, 0-35.9). 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%), arthralgia (20%), and diarrhea (21%). Grade ≥3 TEAEs occurred in 80 (68%) participants. Grade 5 TEAEs occurred in 7 (6%) participants and included death following disease progression in 3 (3%), sepsis 1 (1%), dyspnea 1 (1%), and respiratory failure 2 (2%) participants. 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.

Conclusion:

MK-1026 has promising antitumor activity with a manageable safety profile in participants with CLL/SLL exposed to multiple lines of therapy, including in those who had progression of disease on prior covalent BTKi. Further evaluation of MK-1026 in B-cell malignancies is ongoing.