EHA2021 VIRTUAL

EP784
PRELIMINARY CLINICAL DATA FROM A PHASE 1B STUDY OF MAVORIXAFOR AND IBRUTINIB IN PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA WITH MYD88 AND CXCR4 MUTATIONS

Topic: 18. Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

Keywords: CXCR4 | Ibrutinib | Monoclonal gammopathy | Waldenstrom's macroglobulinemia

Steven Treon[1,2], Christian Buske[3], Sheeba Thomas[4], Andrew Branagan[5], Meletios Dimopoulos[6], Jorge Julio Castillo[7,8], Felix Garzon[9], Weihua Tang[9], Rachel Ronan[9], Sean Seyffert[9], Varun Garg[9], Shariq Ali[9], Art Taveras[9], Adriana Badarau[10], Katarina Zmajkovicova[10], Sabine Maier[10], Barbara Maierhofer[10], Jeffrey Matous[11]

[1] Bing Center for Waldenstrom's Macroglobulinemia Research, Harvard Medical School, Boston, MA, United States
[2] Dana Farber Institute, Harvard Medical School, Boston, MA, United States
[3] Comprehensive Cancer Center and Institute of Experimental Cancer Researc, University of Ulm, Ulm, Germany
[4] Deparatment of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[5] Massacusettes General Hospital Cancer Center, Boston, MA, United States
[6] Department of Clinical Therapeutics, National and Kapodistrian, University of Athens School of Medicine, Athens, Greece
[7] Bing Center for Waldenstrom's Macroglobulinemia, Harvard Medical School, Boston, MA, United States
[8] Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, United States
[9] X4 Pharmaceuticals, Boston, MA, United States
[10] X4 Pharmaceuticals, Vienna, Austria
[11] Colorado Blood Cancer Institute, Sarah Cannon Research Institute, Denver, CO, United States

Background: Waldenström macroglobulinemia (WM) is a rare B-cell lymphoproliferative disorder characterized by increased clonal IgM-secreting cells. Though other covalent and noncovalent BTK inhibitors (BTKi) are in development for WM, ibrutinib is the only BTKi approved by the FDA and EMA for WM. Most patients with WM (>90%) have somatic mutations in *MYD88*, and a subset (≤40%) also have WHIM-like activating mutations in *CXCR4* (*CXCR4*^{WHIM}). The presence of *CXCR4*^{WHIM} impacts response to BTKi in WM, as manifested by delayed response, inferior depth of response, and/or shorter progression-free survival. Inhibition of CXCR4 has been shown to sensitize *CXCR4*^{WHIM}-expressing cells to ibrutinib. Mavorixafor, an oral small-molecule antagonist of CXCR4, has been shown to inhibit CXCL12 binding and ERK hyperactivation for many *CXCR4* mutations in vitro.

Aims: This study examines the safety and efficacy of mavorixafor in combination with ibrutinib in patients with WM with *MYD88* and *CXCR4* mutations.

Methods: This phase 1b, open-label, multicenter, single-arm study (NCT04274738) examines intra-patient dosing, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of mavorixafor in combination with ibrutinib. Eligibility includes age ≥18 years, clinicopathological WM diagnosis, consensus criteria indication for treatment, measurable disease, 0–3 prior therapies, confirmed *MYD88*^{L265P} and *CXCR4*^{WHIM} mutations, and ability to provide written informed consent. Patients are initiated on mavorixafor 200 mg and ibrutinib 420 mg, both oral and once-daily (QD). Mavorixafor escalation to 400 mg occurs after 28 days if no dose-limiting toxicities (DLTs) are observed and to 600 mg after 400 mg is deemed safe (<2/6 DLTs). Patients are followed for adverse events (AEs) and change from baseline in IgM, PK, and PD (peripheral white blood cell [WBC] counts).

Results: At data cutoff (January 22, 2021), 7 patients have enrolled; all continue on study. All 7 patients were escalated to 400 mg, with 6 remaining at 400 mg and 1 de-escalated to 200 mg (median exposure, 90 days). None have yet escalated to 600 mg. A total of 56 AEs were observed (84% grade 1 severity). Of 50 AEs with complete assessment for causal relationship to study drugs, 4 were deemed related to mavorixafor only, 7 to ibrutinib only, and 18 to the combination. A single patient experienced all events attributed to mavorixafor only (all grade ≤2 GI events). Only 1 DLT was observed, consisting of grade 3 hypertension with definitive attribution to ibrutinib and possible attribution to mavorixafor. No AEs led to study discontinuation, and no serious AEs were observed. Six out

of 7 patients showed decrease in IgM after 1 cycle. Four patients were treated for ≥3 cycles; all had decrease in serum IgM, with 2 achieving a ≥50% decrease from baseline consistent with partial response after 3 cycles (median decrease, 51.0%; range, 4.4%–84.5%). Mavorixafor and ibrutinib exposures were consistent with previous reports, and combination treatment increased peripheral lymphocytes, neutrophils, and monocytes.

Summary/Conclusion: Our findings to date in patients with WM carrying both *MYD88* and *CXCR4* mutations show that mavorixafor in combination with ibrutinib is well tolerated at doses up to 400 mg QD. Mavorixafor and ibrutinib exposures were consistent with previous single-agent studies, suggesting no drug–drug interactions, and mavorixafor exposures tracked with increases in key WBC counts. Combination of mavorixafor with ibrutinib led to rapid and clinically meaningful decrease in IgM levels, suggesting that mavorixafor may sensitize $CXCR4^{WHIM}$-expressing cells to BTKi.

Abstract Book Citations: Authors, Title, HemaSphere, 2021;5:(S2):pages. Abstract Book, DOI:
http://dx.doi.org/10.1097/HS9.0000000000000566