Preliminary Clinical Response Data From a Phase 1b Study of Mavorixafor in Combination With Ibrutinib in Patients With Waldenström's Macroglobulinemia With *MYD88* and *CXCR4* Mutations

Steven P. Treon,[1] Christian Buske,[2] Sheeba Thomas,[3] Jorge J. Castillo,[1] Andrew Branagan,[4] Meletios Dimopoulos,[5] Maria Gavriatopoulou,[5] Diego Cadavid,[6] Weihua Tang,[6] Sean Seyffert,[6] Varun Garg,[6] Michael Tillinger,[6] Shariq Ali,[6] Arthur G. Taveras,[6] Kelly Chen,[6] Jeffrey Matous[7]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Comprehensive Cancer Center and Institute of Experimental Cancer Research, University of Ulm, Germany; [3]Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [5]Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [6]X4 Pharmaceuticals, Boston, MA, USA; [7]Colorado Blood Cancer Institute, Sarah Cannon Research Institute, Denver, CO, USA

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Background

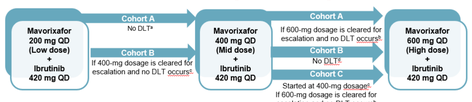
- Waldenström's macroglobulinemia (WM) is a rare, indolent B-cell lymphoproliferative disorder characterized by expansion of clonal immunoglobulin M (IgM)-secreting cells[1]
- Ibrutinib is the first Bruton tyrosine kinase (BTK) inhibitor approved by the US Food and Drug Administration and the European Medicines Agency for WM, recently followed by zanubrutinib in the United States[2,3]
- More than 90% of patients with WM have somatic mutations in *MYD88*, and 30%–40% of these patients have an additional activating mutations in *CXCR4 (CXCR4*^{WHIM}*)*[4-6]
- *CXCR4*^{WHIM} in WM is associated with higher serum IgM level, symptomatic hyperviscosity, earlier time to treatment, and inferior response to approved and investigational BTK inhibitors compared to individuals with *CXCR4*^{WT} WM[5,7,8]
- Inhibition of CXCR4 has been shown to sensitize CXCR4^{WHIM}-expressing WM cells to ibrutinib[9]
- Mavorixafor is an oral, small-molecule antagonist of CXCR4. *In vitro* data with MWCL-1 WM cells have shown that mavorixafor enhances efficacy of BTK inhibitors by overcoming the protective effect of bone marrow stroma on tumor cells in WM[10]
- Here we report an early assessment of the combination of mavorixafor and ibrutinib treatment on immunoglobulin M (IgM) and hemoglobin (Hgb) levels, safety, and clinical response in patients with *MYD88* and *CXCR4*^{WHIM} WM

Methods

- This ongoing phase 1b, open-label, multicenter, single-arm study (NCT04274738) is examining intrapatient dose escalation, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of mavorixafor in combination with ibrutinib (target N=18)
- Eligibility includes age ≥18 years, clinicopathological WM diagnosis, consensus criteria indication for treatment, measurable disease, 0–3 prior therapies, and confirmed *MYD88* and *CXCR4*^{WHIM} mutations
- Patients in Cohorts A and B are initiated on mavorixafor 200 mg once daily (QD; low-dose), and patients in Cohort C are initiated on mavorixafor 400 mg QD (mid-dose), along with oral ibrutinib 420 mg QD in all cohorts
- Mavorixafor escalation to 400 mg (mid-dose) occurs after 28 days if no dose-limiting toxicities (DLTs) are observed in 5/6 participants and to 600 mg (high-dose) after 400 mg is deemed safe (<2/6 DLTs) (Figure 1)
- Patients are followed for adverse events (AEs), and change from baseline in IgM, Hgb, PK, and clinical responses

Figure 1. Study Design (NCT04274738)

Each treatment cycle is 28 days



[a]If DLT occurs, patient is withdrawn from study.
[b]If dose escalation not cleared, patient remains at current dose level. If dose escalation is cleared but DLT occurs, patient stays in the study after dose de-escalation.
[c]If dose escalation is not cleared, patient remains at current dose level. If dose escalation is cleared but DLT occurs, patient is withdrawn.
[d]If DLT occurs, patient stays in the study after dose de-escalation.
Cohort A will continue to receive 400 mg until 600 mg is deemed tolerable by Cohort B. Once 600 mg is deemed tolerable, all enrolled patient doses may escalate to 600 mg, and Cohort C will start at 400 mg and their doses will escalate to 600 mg.

Objectives of the Study

- To establish a pharmacologically active dose of mavorixafor in combination with ibrutinib based on pooled safety, clinical response, PK, and PD data
- To assess clinical outcome, including changes in serum IgM and Hgb over time
- To assess major response rate (defined as complete response [CR] + very good partial response [VGPR] + partial response [PR]) over time
- To assess the safety profile of the combination of mavorixafor and ibrutinib
- To evaluate the effect of treatment with mavorixafor in combination with ibrutinib on selected PD and disease-related biomarkers

Early data analysis was performed with data cutoff at October 12, 2021

Results

Patient disposition and baseline characteristics

- Patient disposition as of October 12, 2021 is shown in Figure 2
- 16 patients have enrolled in the study (Table 1), with 14 having dosing information as of the data cut.
- Median duration of treatment was 272.5 days (range, 33–435 days) as of the cutoff date (n=14)
- 4 patients have withdrawn; 12 patients remain on study
- In this report, response and tolerability data for the 14 patients for whom dosing information was available as of the data cutoff are provided

Figure 2. Patient Disposition

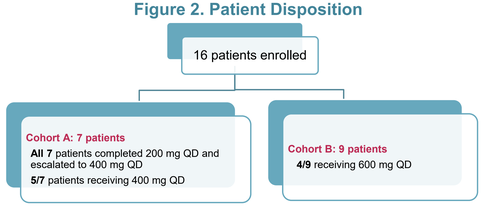


Table 1. Demographics, Clinical Characteristics, and Mutational Status of All Patients (N=16)

Characteristic	
Both *MYD88* and *CXCR4* mutations, n (%)	16 (100)
Median age (range), y	71.5 (38–83)
Male sex, n (%)	11 (69)
Median disease duration (range), y	2.5 (0–14)
Frontline therapy, n (%)	7 (43.7)
Relapse/refractory therapy, n (%)	9 (56.3)
Median baseline IgM levels[a], g/L	46.68
Median baseline hemoglobin levels[b], g/L	103
Median baseline platelet count[c], × 10^9/L	199
Baseline extramedullary disease, n (%)	3 (19)
Baseline IPSS WM score, n (%)	
Low	3 (19)
Intermediate	6 (38)
High	7 (44)
CXCR4 mutational status, n (%)	
Frameshift mutation	7 (44)
Nonsense mutation	9 (56)

IPSS, International Prognostic Scoring System.
[a]Normal range, 0.5–2 g/L.
[b]Normal range: male, 138–172 g/L; female, 121–151 g/L.
[c]Normal range, 150–400×10^9/L.

Overall the combination of mavorixafor and ibrutinib was tolerable based on findings to date[a]

- 11 participants reported 136 treatment-emergent AEs (TEAEs)
- 70% of AEs were mild (Common Terminology Criteria for Adverse Events grade 1)
- 4 participants discontinued early: 1 had worsening pain in bilateral shoulders, elbows, and wrists after cycle 6 400-mg dose, 1 had dysphagia after cycle 1 200-mg dose, 1 had fatigue after cycle 1 200-mg dose, 1 had serious AE of pneumonia and sepsis resulting in death after cycle 1, 200-mg dose
- 7 DLT AEs were reported in 3 patients (Table 2)
- 6 serious AEs were reported in 2 patients (Table 2)
- 2 serious AEs in 1 patient were fatal[b] (Table 2)

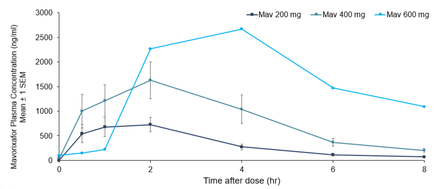
Table 2. DLT AEs[c]

Participant	Age, y	Duration of Treatment in Study, wk	AE	Drug Discontinued	Serious	Grade	Outcome	Investigator-Determined Causality
1	76	63.3	Hypertension	No	No	3	Recovered	Possibly combination therapy
2	71	22.1	Atrial fibrillation	No	Yes	3	Recovered	Possibly ibrutinib
			Atrial fibrillation	No	Yes	3	Recovered	Possibly combination therapy
			Cryptococcal pneumonia	No	Yes	3	Recovered	Probably combination therapy
			Cryptococcal brain abscess	No	Yes	3	Recovered	Probably combination therapy
3	81	3.9	Pneumonia	Yes	Yes	5	Fatal	Possibly combination therapy
			Sepsis	Yes	Yes	5	Fatal	Possibly combination therapy

[a]Includes data beyond the October 12, 2021, cutoff (ie, through October 28, 2021).
[b]Patient had long standing WM, autoimmune disorders (polymyalgia rheumatica [PMR], Crohn's disease), was previously treated with bendamustine plus rituximab and maintenance rituximab that was stopped due to recurring upper respiratory tract infections. Presented with hyperviscosity and progressive anemia and required plasmapheresis prior to study.
[c]DLT in participant 1 was on 400 mg mavorixafor QD. DLTs in participants 2 and 3 were on the 200-mg QD mavorixafor dose level (after 400 mg cleared). DLTs in participant 3 was post data-cut.

Dose-dependent increases in plasma levels of mavorixafor

Figure 3. Plasma Levels of Mavorixafor[a]

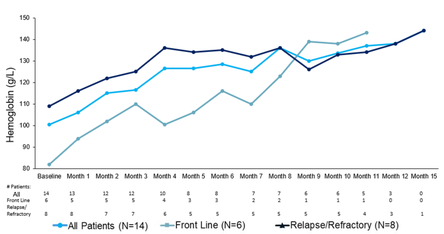


[a]Interim early data analysis performed with data cutoff at August 15, 2021.

- Mavorixafor and ibrutinib exposures were consistent with previous single-agent studies[11,12]
- No apparent drug–drug interactions between mavorixafor and ibrutinib were observed

Median Hgb increased toward normal over time

Figure 4. Median Change From Baseline in Hgb[a,b]

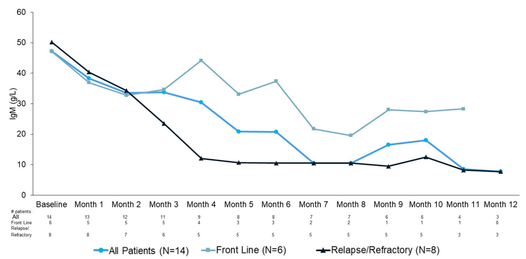


[a]Interim early data analysis performed with data cutoff at Oct 12, 2021.
[b]Missing data imputed using last observation carried forward.

- Median Hgb increased by ~38 g/L from baseline to month 12 (Figure 4)

Serum IgM levels decreased over time during dose escalation

Figure 5A. Median Serum IgM Levels[a,b]

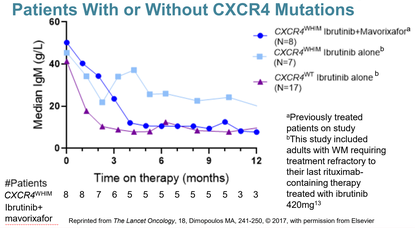


[a]Data cut as of October 12, 2021.
[b]For 1 participant receiving frontline therapy, study treatment was temporarily withheld due to an AE the week prior to Month 4 IgM sample collection; the subject subsequently restarted on a reduced dose and then discontinued from the study at Month 6. Another participant discontinued study treatment after Month 2.

- Overall, all patients showed decrease in serum IgM from baseline while on treatment. For all patients treated for 6 months or longer, median absolute serum IgM level decreased from 47.2 g/L at baseline to 20.8 g/L at 6 months (n=8) and 7.73 g/L at 12 months (n=3) (Figure 5A)

Greater decreases in serum IgM levels were seen after treatment with combination therapy (ibrutinib and mavorixafor) compared to decreases seen with ibrutinib monotherapy in a previous study of heavily pretreated patients[13]

Figure 5C. Serum IgM Levels After Treatment with Combination Therapy vs. Ibrutinib Monotherapy in Patients With or Without CXCR4 Mutations



[a]Previously treated patients on study
[b]This study included adults with WM requiring treatment refractory to their last rituximab-containing therapy treated with ibrutinib 420mg[13]

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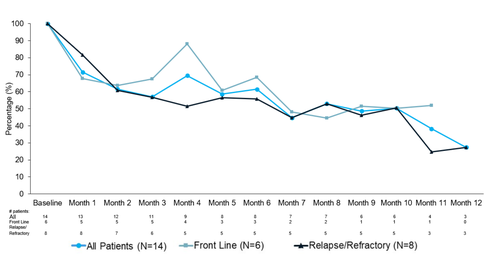
Figure 5B. Median IgM Levels Normalized to Baseline[a,b]



- All patients showed decrease in serum IgM from baseline (Figure 5B)

Overall response rate (ORR) for evaluable patients (minor response [MR] or better) was 100% (N=10)[a]

Table 3. Clinical Response Rates

Response Category	Overall (n=10)	Frontline (n=3)	Relapse/Refractory (n=7)
ORR, n (%)	10 (100)	3 (100)	7 (100)
Major response (CR+VGPR+PR), n (%)	4 (40)	1 (33)	3 (43)
VGPR n (%)	1 (10)	0 (0)	1 (14)
PR n (%)	3 (30)	1 (33)	2 (29)
MR n (%)	6 (60)	2 (67)	4 (57)

[a]Data cut as of October 12, 2021. Four patients have not reached adequate follow-up time (≥3 months post-treatment) at this data cutoff for evaluation of clinical response.

- Of 10 evaluable patients, 4 achieved major response, of whom 1 achieved a VGPR, and 3 achieved PR (Table 3)

Conclusions

- Overall, mavorixafor in combination with ibrutinib (420 mg) was tolerated with manageable safety profile in patients with WM with *MYD88* and *CXCR4*^{WHIM} mutations, with cohorts completing the low (200-mg) and mid (400-mg) QD levels; dose escalation at the highest (600-mg) QD level continues
- Mavorixafor and ibrutinib exposures were consistent with previous single-agent studies, suggesting no drug–drug interactions
- ORR was 100% in all evaluable patients, with 40% achieving major response, including 10% VGPR attainment as of data cutoff Oct 12, 2021, with additional patients continuing to show decreases in IgM
- Combination of mavorixafor with ibrutinib led to rapid, clinically meaningful, and durable decrease in IgM levels and increase in Hgb levels
- Greater decreases in serum IgM levels were seen after treatment with combination therapy (ibrutinib and mavorixafor) compared to decreases seen with ibrutinib monotherapy in a previous study
- Emerging data from this ongoing study inform on the safety, tolerability, and efficacy of combining ibrutinib with mavorixafor to improve responses in patients with WM with *MYD88* and *CXCR4*^{WHIM} mutations

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Disclosures

SPT is a current employee of the Dana Farber Cancer Institute and holder of multiple patents related to testing and treatment of MYD88- and CXCR4-mutated B-cell malignancies. He has served as a consultant for Pharmacyclics, AbbVie, Janssen, BeiGene, and X4 and has received research funding from Pharmacyclics, AbbVie, Janssen, BeiGene, Eli Lilly, and Bristol Myers Squibb. **CB** has received research funding from Amgen, Roche, Janssen, Bayer, Merck Sharp & Dohme corp., and Celltrion, honoraria from Roche, Janssen, Bayer, Merck Sharp & Dohme corp., Celltrion, Pfizer, and Novartis. CB is also on the speaker bureau for Roche, Janssen, Bayer, Merck Sharp & Dohme corp., Celltrion, and Pfizer, and is a member of the board of directors or on the advisory committee of Roche, Janssen, Bayer, Merck Sharp & Dohme corp., Celltrion, and Novartis. **ST** has received research funding from X4 Pharmaceuticals, Bristol Myers Squibb, Genentech, Ascentage Pharma, and Acerta Pharma, and is a member of the board of directors or advisory committee of BeiGen and Pharmacyclics. **JJC** has served as a consultant for and received research funding from AbbVie, BeiGene, Pharmacyclics, Janssen, Roche, and TG Therapeutics. **AB** is a member of the board of directors or on the advisory committee of BeiGene, Sanofi-Genzyme, Karyopharm, and Pharmacyclics. **MD** has received honoraria from Amgen, Takeda, Janssen, Bristol Myers Squibb, and BeiGene. **MG** has nothing to disclose. **DC** is an employee of and possesses equity ownership of X4 Pharmaceuticals. **FG** has served as a consultant for X4 Pharmaceuticals. **WT, SS, VG, MT, SA, AGT,** and **KC** are employees of and/or possess equity ownership of X4 Pharmaceuticals. **JM** is a member of the board of directors or advisory committee for Janssen and Pharmacyclics.

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