Oral Administration of Mavorixafor, a CXCR4 Antagonist, Increases Peripheral White Blood Cell Counts Across Different Disease States

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Poster # 2186

Background

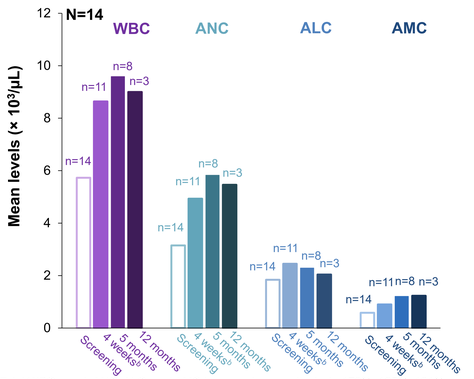
- Neutropenia, lymphocytopenia, and monocytopenia are common features of many diseases and may increase susceptibility to common and opportunistic infections
- The CXCR4/CXCL12 chemokine receptor axis regulates the trafficking of all 3 types of leukocytes between the bone marrow, blood and lymphatic organs[1]
- Mavorixafor is an orally available, investigational, small-molecule, selective antagonist of the CXCR4 receptor. It is under investigation as a treatment for immunodeficiency diseases and to inhibit CXCR4-mediated tumor survival in malignancies[2-5]
- Our ongoing studies in Waldenström's macroglobulinemia (WM), renal cell carcinoma, WHIM (Warts, Hypogammaglobulinemia, Infections, Myelokathexis) syndrome, and chronic idiopathic neutropenia show that daily oral administration of mavorixafor increases blood neutrophils, lymphocytes, and monocytes, with short-term or long-term treatment

Waldenström's Macroglobulinemia

This ongoing phase 1b trial (NCT04274738) evaluates mavorixafor (200–600 mg once daily [QD]) in combination with ibrutinib (420 mg QD) in patients with WM with *MYD88* and *CXCR4* mutations

In an early analysis, treatment with mavorixafor in combination with ibrutinib increased white blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and absolute monocyte count (AMC) 4 weeks after treatment that was sustained at 12 months

Figure 1. Improvements in Peripheral WBC Counts[a] and WBC Subtypes in Patients With WM With *MYD88* and *CXCR4* Mutations Treated With Combination of Mavorixafor and Ibrutinib



[a]Total WBC count, ANC, ALC, and AMC increased, respectively, to 173%, 165%, 181%, and 196% of pretreatment after 4 weeks, with increases sustained at 159%, 162%, 133%, and 246% of pretreatment at 12 months (Early data cutoff Oct 12, 2021).
[b]Data for 4 weeks calculated using mean postdose values while all other timepoints use predose trough values.

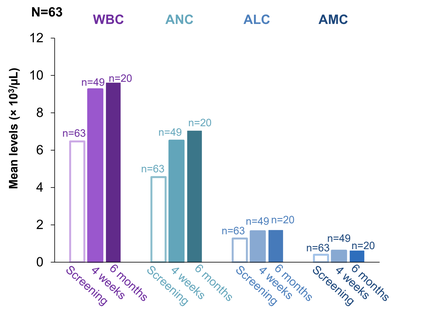
- Short-term increases in peripheral lymphocytes have been shown to occur with ibrutinib monotherapy in WM[6]

Advanced Clear Cell Renal Cell Carcinoma (ccRCC)

This ongoing phase 1/2 trial (NCT02667886) evaluates the safety and tolerability of escalating doses of mavorixafor (200–600 mg QD) in combination with axitinib (5 mg twice daily) in patients with advanced ccRCC who received ≥1 prior therapy

Treatment with mavorixafor in combination with axitinib increased WBC, ANC, ALC, and AMC 4 weeks after treatment that was sustained at 6 months

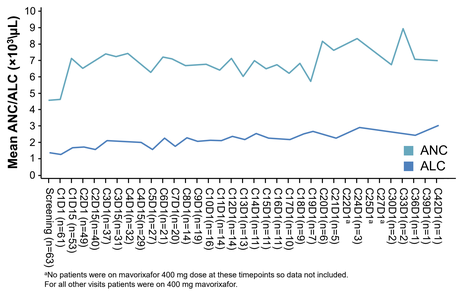
Figure 2. Improvements in Peripheral WBC Counts[a] and WBC Subtypes in Patients With Advanced ccRCC Treated With Combination of Mavorixafor and Axitinib



[a]Total WBC count, ANC, ALC, and AMC increased respectively to 153%, 158%, 143%, and 182% of pretreatment after 4 weeks with increases sustained at 159%, 171%, 139% and 166% of pretreatment after 6 months' treatment.

Additionally, treatment with mavorixafor in combination with axitinib resulted in long-term sustained increases in ANC and ALC over 4 years

Figure 3. Long-term Improvements in ANC and ALC in Patients With ccRCC Treated With Combination of Mavorixafor and Axitinib



[a]No patients were on mavorixafor 400 mg dose at these timepoints so data not included. For all other visits patients were on 400 mg mavorixafor.

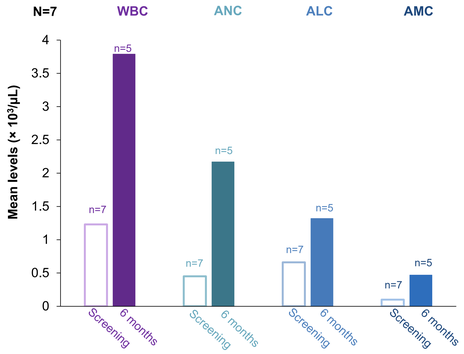
- Similar results were reported in in a study evaluating mavorixafor in combination with nivolumab in metastatic ccRCC (NCT02923531)

WHIM Syndrome

This phase 2 trial (NCT03005327) evaluated the safety and tolerability of escalating doses of mavorixafor (50–400 mg QD) in adults with WHIM syndrome

Sustained increases in WBC count, ANC, ALC, and AMC were seen with 6 months of mavorixafor treatment in adults with WHIM syndrome

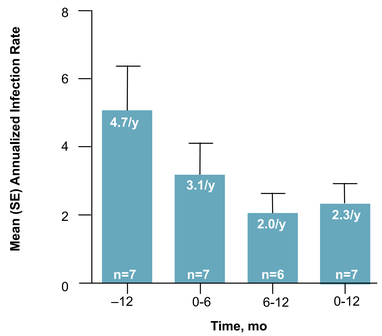
Figure 4A. Improvements in Peripheral WBC Counts[a] and WBC Subtypes After Treatment With Mavorixafor



[a]Total WBC count, ANC, ALC, and AMC increased after the first dose of mavorixafor with increases sustained at 339%, 652%, 239%, and 486% respectively of pretreatment after 6 months' treatment.
Data calculated using average of post-dose dense sampling time points.

Sustained increases in leukocyte counts were accompanied by decreased annualized infection rates

Figure 4B. Annualized Infection Rates Before and After Treatment With Mavorixafor

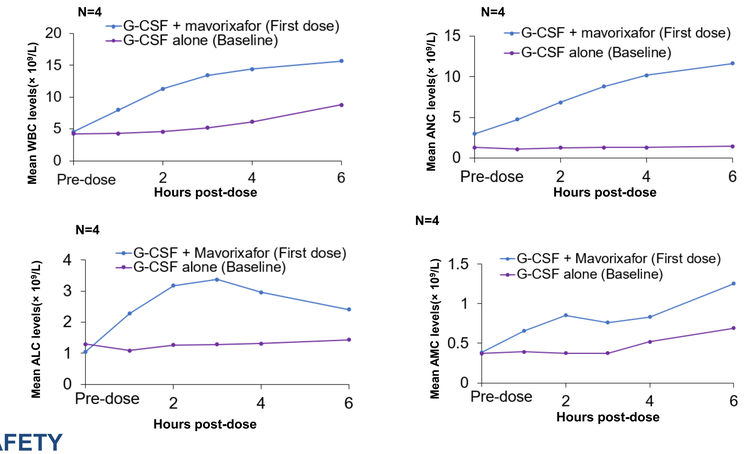


Chronic Neutropenia Disorders

- This ongoing phase 1b, open-label, multicenter trial (NCT04154488) evaluates mavorixafor (400 mg QD) in patients with severe congenital neutropenia or chronic neutropenia disorders
- Congenital neutropenia is defined as any congenital neutropenia, regardless of mutation, presenting with an ANC <1000 cells/μL. Chronic idiopathic neutropenia is defined as an ANC<1000 cells/μL for ≥6 months and not attributable to drugs, specific genetic, infectious, inflammatory, autoimmune, or malignant cause

Treatment with a single dose of mavorixafor increased WBC count, ANC, ALC, and AMC in adults with chronic neutropenia receiving concomitant granulocyte colony-stimulating factor (G-CSF) therapy

Figure 5. Improvements in Peripheral WBC Counts and WBC Subtypes Following a Single Dose of Mavorixafor



SAFETY

Mavorixafor has been generally well tolerated, with a manageable safety profile across various disease states (ccRCC, WM, WHIM Syndrome, and chronic neutropenia disorders) either alone or in combination with oncology drugs

Conclusions

- Mavorixafor is an orally available CXCR4 antagonist now in phase 1b, phase 2 and phase 3 clinical trials
- Mavorixafor in combination with axitinib, ibrutinib, or G-CSF increased ANC, ALC, and AMC in studies in patients with advanced renal cell carcinoma, WM, and chronic idiopathic neutropenia, respectively. Daily mavorixafor treatment for >1 year showed continuation of these effects, no loss of effectiveness, and a favorable safety profile
- WHIM syndrome is an immunodeficiency disorder due to gain-of-function mutations in *CXCR4*. A phase 2 study of daily oral mavorixafor showed consistent increases in WBC count, ANC, ALC, and AMC associated with decreased infections and warts
- The results of these clinical trials point to the importance of CXCR4-CXCL12 axis in immunity and the potential of mavorixafor to enhance host defenses against infections

Acknowledgements

The authors would like to thank the study participants, study sites, vendors, and everyone involved in the clinical trials and the clinical development of mavorixafor and acknowledge the medical writing assistance of PRECISIONscientia in Yardley, PA, USA, which was supported financially by X4 Pharmaceuticals in compliance with international Good Publication Practice guidelines. The authors acknowledge the contribution of Ashish Bhandari to this study. Ibrutinib was provided by Pharmacyclics LLC, an AbbVie Company.

Disclosures

DCD has served as a consultant for and has received research funding and honoraria from X4 Pharmaceuticals. **SPT** has served as a consultant for and has received research funding from Pharmacyclics, AbbVie, Janssen, BeiGene, BMS, and is a holder of multiple patents related to testing and treatment of *MYD88*- and *CXCR4*-mutated B-cell malignancies. **DFM** has served as a consultant for and received honoraria from BMS, Pfizer, Merck, Alkermes Inc, EMD Serono, Eli Lilly and Company, Iovance, Eisai Inc, Werewolf Therapeutics, Calithera Biosciences, and Johnson and Johnson, as well as research support from BMS, Merck, Genentech, Pfizer, Exelixis, X4 Pharmaceuticals, and Alkermes Inc. **DC** is employed by and possesses equity ownership in X4 Pharmaceuticals. **XL** is a contractor and consultant with X4 Pharmaceuticals. **VG, WT, YH, HJ, KC,** and **AGT** are employed by and/or possess equity ownership in X4 Pharmaceuticals. **JD** is a member of the Board of Directors or advisory committee of X4 Pharmaceuticals, and has served as a consultant and received an honoraria from X4 Pharmaceuticals.

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