Administration of Mavorixafor, an Orally Available CXCR4 Antagonist, Increases Total White Blood Cell, Neutrophil, Lymphocyte, and Monocyte Counts Across Different Disease States

David C. Dale,[1,*] David F. McDermott,[2] Diego Cadavid,[3] Kelly Walkovich,[4] Julia T. Warren,[5] Jeffrey Matous,[6] Xia Luo,[3] Weihua Tang,[3] Honghua Jiang,[3] Kelly Chen,[3] Arthur G. Taveras,[3] Michael Tilinger,[3] Yanping Hu,[3] Jean Donadieu[7,8]

[1]Department of Medicine, University of Washington, Seattle, WA, USA; [2]Beth Israel Deaconess Medical Center, Boston, MA, USA; [3]X4 Pharmaceuticals, Boston, MA, USA; [4]University of Michigan, Ann Arbor, MI, USA; [5]Division of Hematology-Oncology, Department of Pediatrics, Washington University, St. Louis, MO, USA; [6]Colorado Blood Cancer Institute, Sarah Cannon Research Institute, Denver, CO, USA; [7]Department of Pediatric Hematology-Oncology, Reference Center for Chronic Neutropenia, National Registry of Congenital Neutropenia, Paris, France; [8]Sorbonne University, Armand Trousseau Hospital APHP, Paris, France

Disclosures

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Oral CXCR4 Antagonist Mavorixafor Is Under Investigation in Clinical Trials for Various Disease States

- Leukopenia, including neutropenia, lymphocytopenia, and monocytopenia, is a common feature of many diseases and may lead to increased susceptibility to common and opportunistic infections in affected individuals[1-3]
- The CXCR4/CXCL12 chemokine receptor axis plays an important role in regulating leukocytes trafficking between the bone marrow, blood, and lymphatic organs[2,4-6]
- Mavorixafor is an investigational, orally available, small-molecule, selective CXCR4 antagonist. It is under investigation as a treatment for immunodeficiency diseases and to inhibit CXCR4-mediated tumor survival in malignancies, including[1,7-12]:

WHIM syndrome

Chronic neutropenic disorders (CNDs)

Congenital, cyclic, and chronic idiopathic neutropenia

Oncology

WM, ccRCC[a]

- Here, we report the effect of daily oral administration of mavorixafor on peripheral WBC counts and differential leukocyte counts in study participants with WHIM syndrome, CNDs, WM, and ccRCC

ccRCC, clear cell renal cell carcinoma; CND, chronic neutropenic disorder; WBC, white blood cell; WHIM, Warts, Hypogammaglobulinemia, Infections, Myelokathexis; WM, Waldenström's macroglobulinemia.

[a]Clinical trials evaluating mavorixafor in combination therapy in patients with ccRCC have been completed.

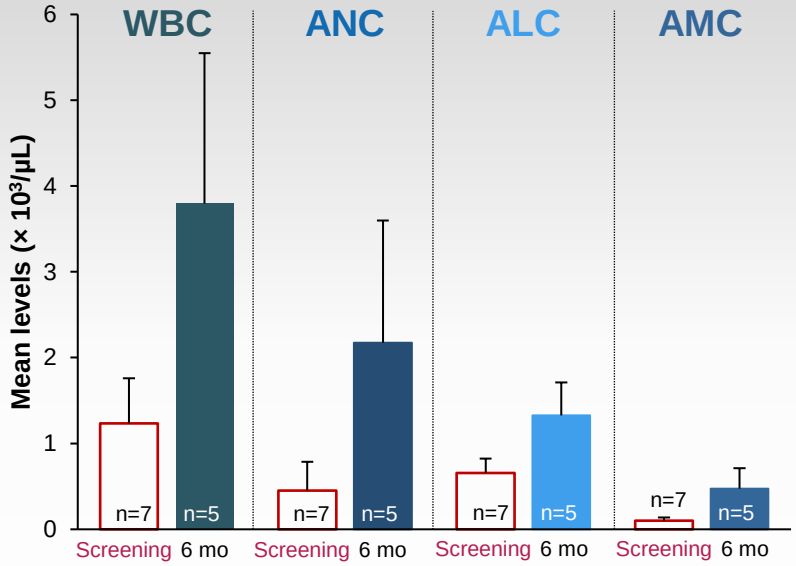
1. Dale DC, et al. *Blood*. 2020;136(26):2994-3003. **2.** McDermott DH, Murphy PM. *Immunol Rev*. 2019;287(1):91-102. **3.** Dale C, et al. Oral administration of mavorixafor, a CXCR4 antagonist, increases peripheral white blood cell counts across different states. Oral presentation presented at the 63rd American Society of Hematology Annual Meeting & Exposition; December 11–14, 2021. **4.** Heusinkveld LE, et al. *Expert Opin Orphan Drugs*. 2017;5(10):813-825. **5.** Bachelerie F. *Dis Markers*. 2010;29(3-4):189-198. **6.** Badolato R, et al. *Blood*. 2017;130(23):2491-2498. **7.** ClinicalTrials.gov. NCT03995108. Updated October 6, 2021. Accessed September 1, 2022. **8.** ClinicalTrials.gov. NCT03005327**.** Updated August 20, 2021. Accessed September 1, 2022. **9.** ClinicalTrials.gov. NCT04274738. Updated May 17, 2022. Accessed September 1, 2022. **10.** ClinicalTrials.gov. NCT04154488. Updated May 25, 2022. Accessed September 1, 2022. **11.** ClinicalTrials.gov. NCT02667886. Updated September 22, 2021. Accessed September 1, 2022. **12**. ClinicalTrials.gov. NCT02923531. Updated August 1, 2019. Accessed September 1, 2022.

WHIM Syndrome

Improvements Were Observed in Hematological Parameters and Infection Rates With Mavorixafor Treatment in a Phase 2 Trial

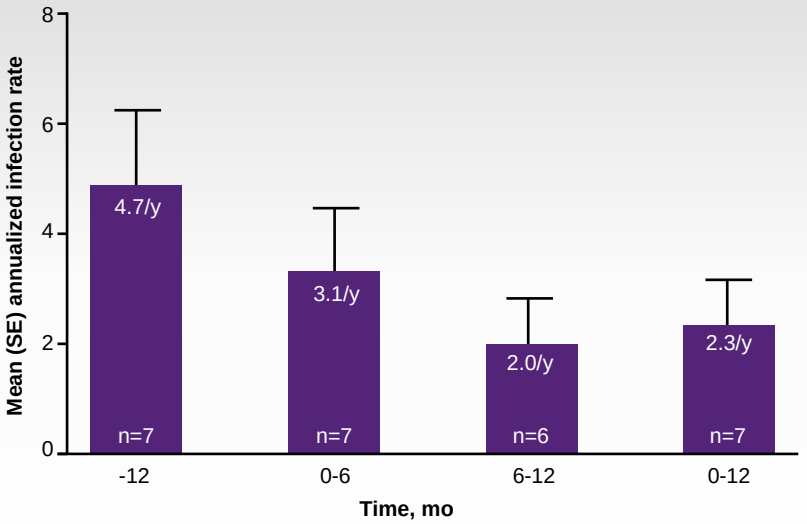
A phase 2 trial (NCT03005327) evaluated the safety and tolerability of escalating doses of mavorixafor (50–400 mg QD) in adults with WHIM syndrome.[1] Mavorixafor is currently being evaluated in adolescents and adults in an ongoing phase 3 trial (NCT03995108)[2]

Peripheral WBC[a] and Differential Leukocyte Counts After Treatment With Mavorixafor (N=7)[3]



WBC count, ANC, ALC, and AMC increased after the first dose of mavorixafor with increases sustained after 6 months of treatment[3]

Annualized Infection Rates Before and After Treatment With Mavorixafor[4]



Sustained increases in leukocyte counts were accompanied by decreased annualized infection rates[4]

ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; QD, once daily; SE, standard error.
[a]Data calculated using average of postdose dense sampling time points.

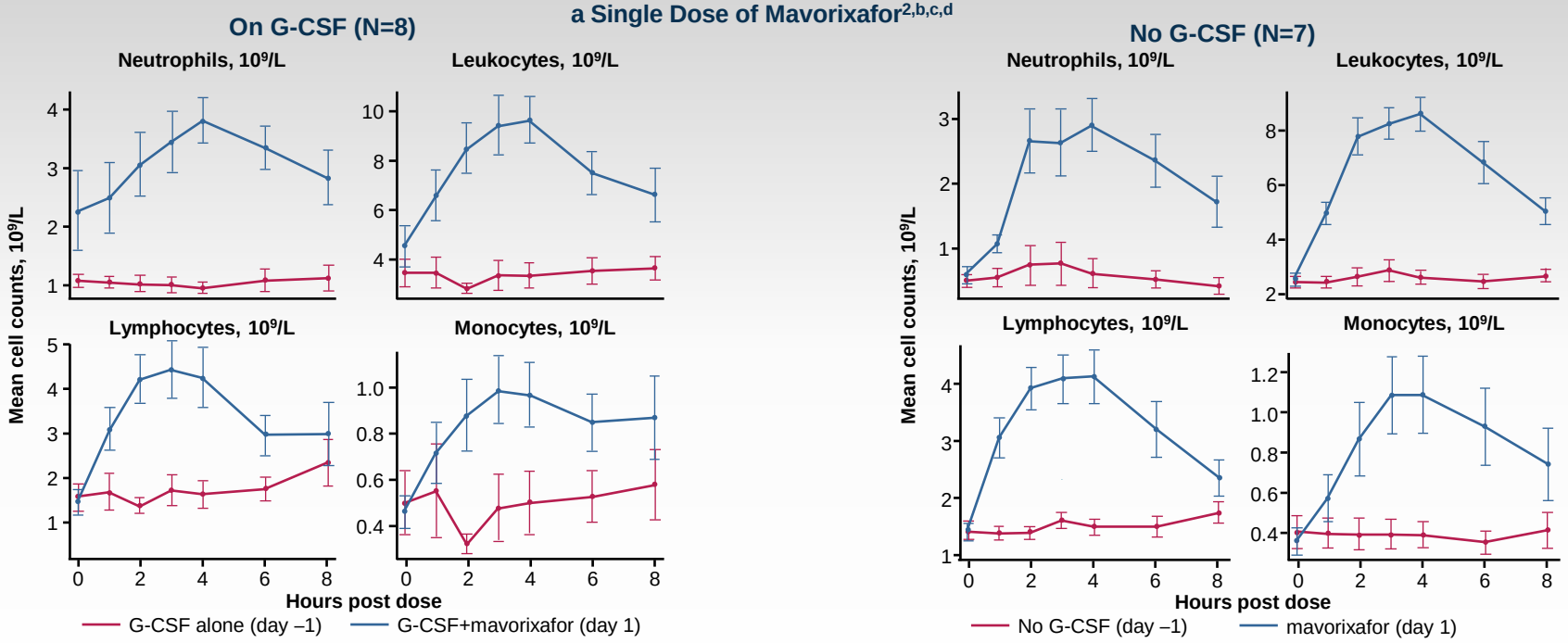
1. ClinicalTrials.gov. ClinicalTrials.gov identifier: NCT03005327. Updated August 20, 2021. Accessed September 7, 2022. https://clinicaltrials.gov/ct2/show/NCT03005327. **2.** ClinicalTrials.gov. ClinicalTrials.gov identifier: NCT03995108. Updated August 20, 2021. Accessed September 7, 2022. https://clinicaltrials.gov/ct2/show/NCT03995108. **3.** Data on File. X4 Pharmaceuticals, Inc., Boston, MA. **4.** Dale C, et al. Oral administration of mavorixafor, a CXCR4 antagonist, increases peripheral white blood cell counts across different states. Oral presentation presented at the 63rd American Society of Hematology Annual Meeting & Exposition; December 11–14, 2021.

Chronic Neutropenic Disorders

Increases in WBC Counts Were Observed With a Single Dose of Mavorixafor

An ongoing phase 1b, open-label, multicenter trial (NCT04154488) evaluating the safety, tolerability, and early efficacy of mavorixafor (400 mg once daily) alone or with concurrent G-CSF use across CNDs[1,a]

Peripheral WBC and Differential Leukocyte Counts on Day –1 Versus Day 1 in Participants ± G-CSF Use Following a Single Dose of Mavorixafor[2,b,c,d]



Error bars represent 1 unit of standard error of the mean.

Treatment with a single dose of mavorixafor increased WBC count, ANC, ALC, and AMC in adults with CNDs, regardless of concurrent G-CSF use[2,c]

G-CSF, granulocyte colony–stimulating factor.

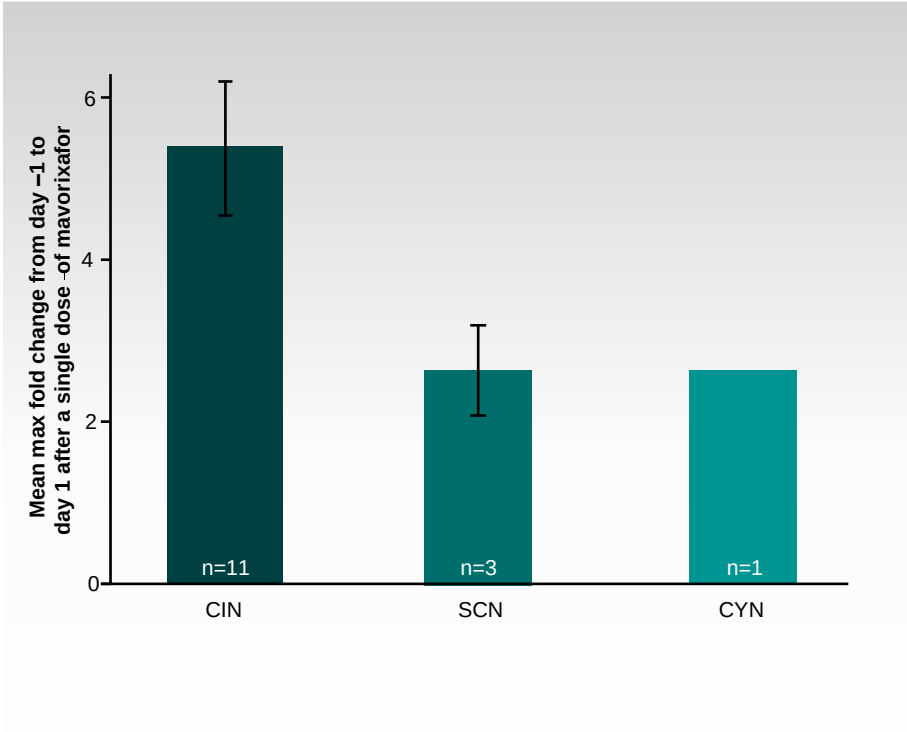
[a]Enrolled patients were diagnosed with chronic idiopathic, congenital, or cyclic neutropenia ≥6 months prior and ANC <1000/µL at screening visits or on G-CSF with ANC >1000/µL. [b]Hematologic parameters were recorded over 6 to 8 hours 1 day before receiving mavorixafor (day –1) and on the first day of mavorixafor treatment (day 1).[2] [c]Data cutoff June 21, 2022[2] [d]In the overall cohort, total WBC count, ANC, ALC, and AMC increased to 323%, 489%, 307%, and 309%, respectively, of the baseline values at peak over 6 to 8 hours after 1 dose.[2]

1. ClinicalTrials.gov. ClinicalTrials.gov identifier: NCT04274738. Updated May 17, 2022. Accessed September 14, 2022. https://clinicaltrials.gov/ct2/show/NCT04274738.
2. Data on File. X4 Pharmaceuticals, Inc., Boston, MA.

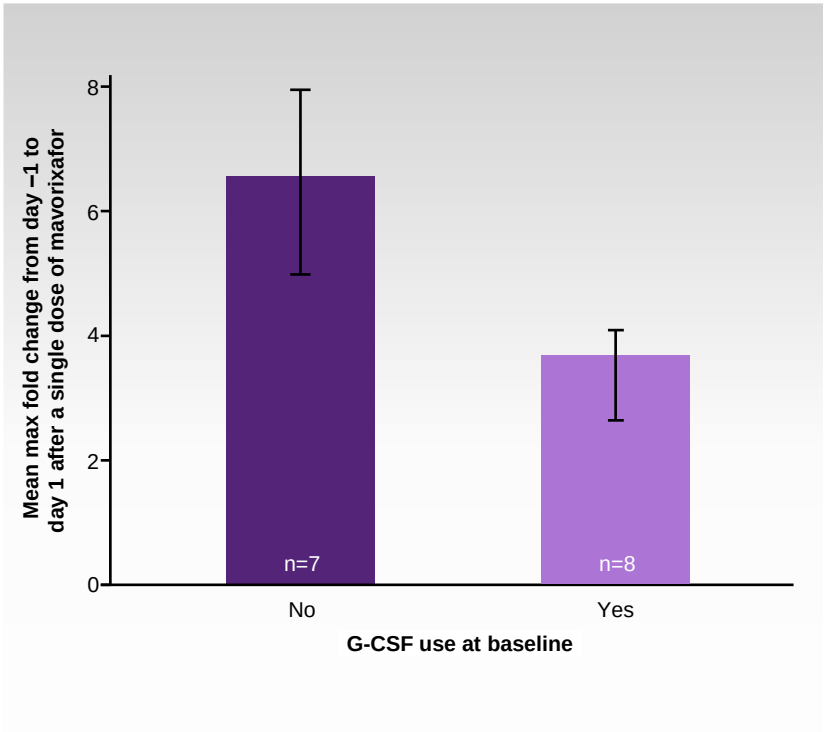
Chronic Neutropenic Disorders

Fold Change by Type of Chronic Neutropenic Disorders and G-CSF Use

Mean maximum fold change in ANC by type of CNDs (n=15)[a]



Mean maximum fold change in ANC by G-CSF use (n=15)[a]



- Treatment with a single dose of mavorixafor increased the ANC level from day –1 regardless of neutropenia subtype examined or concurrent G-CSF use
- Treatment-emergent AEs (n=11) were all grade 1, with no serious AEs reported and good tolerability

AE, adverse event; CIN, chronic idiopathic neutropenia; CND, chronic neutropenic disorders; CYN, cyclic neutropenia; G-CSF, granulocyte-colony stimulating factor; SCN, severe congenital neutropenia.

[a]Data cutoff June 21, 2022

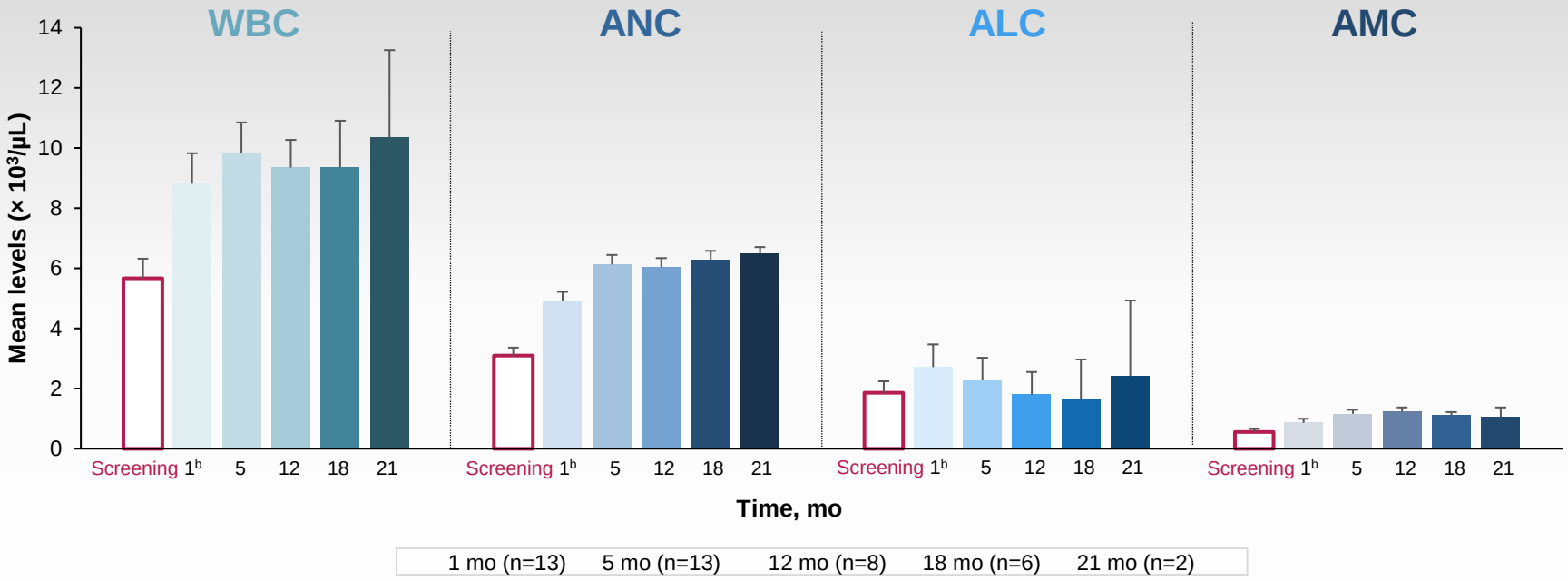
Data on File. X4 Pharmaceuticals, Inc., Boston, MA.

Waldenström's Macroglobulinemia

Sustained Improvements in Hematological Parameters Were Observed With Mavorixafor in Combination With Ibrutinib

An ongoing phase 1b trial (NCT04274738) evaluates mavorixafor (200–600 mg QD) in combination with ibrutinib (420 mg QD) in participants with WM with *MYD88* and *CXCR4* variants[1]

Improvements in Peripheral WBC and Differential Leukocyte Counts in Participants With WM With MYD88 and CXCR4 Variants Treated With Combination of Mavorixafor and Ibrutinib[2] (N=16)[a]



Data from an interim analysis show treatment with mavorixafor in combination with ibrutinib increased WBC count, ANC, ALC, and AMC to 175%, 167%, 186%, and 190% of screening values, respectively, 4 weeks after treatment with increases sustained at 228%, 266%, 178%, and 190% at 21 months[2]

ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; WM, Waldenström's macroglobulinemia; WBC, white blood cell.
[a]Data cutoff May 19, 2022. [b]Data for 4 weeks were calculated using mean postdose values while all other timepoints use predose trough values.

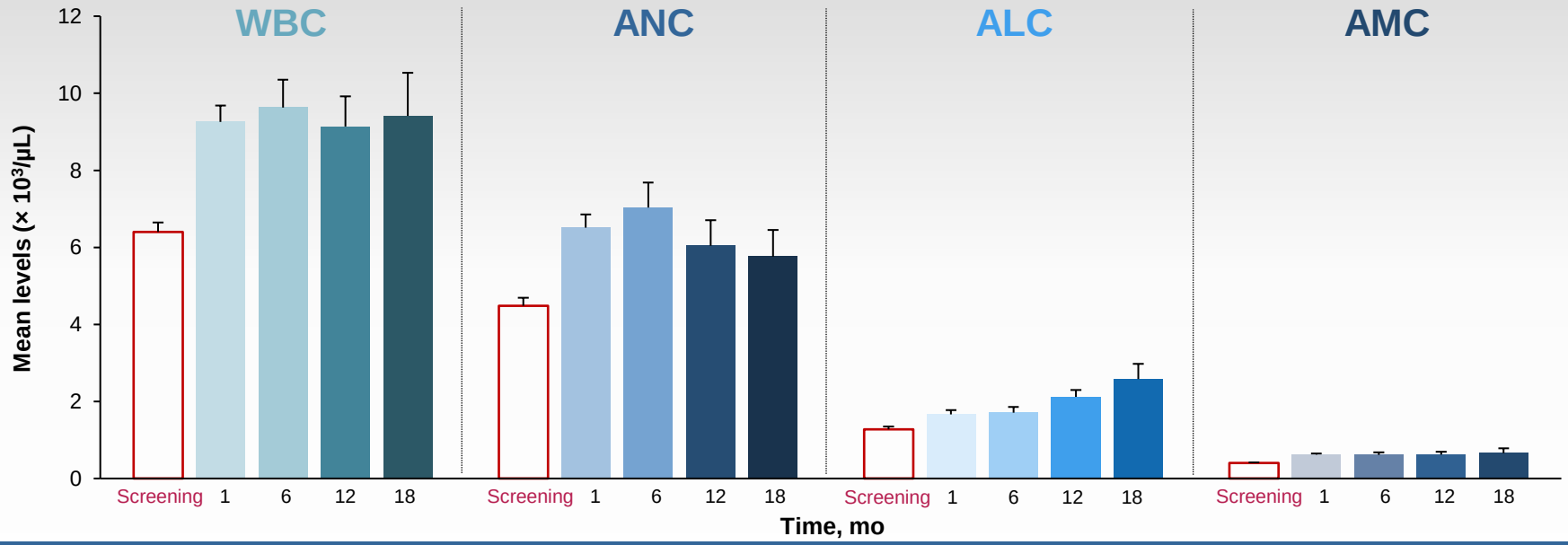
1. ClinicalTrials.gov. ClinicalTrials.gov identifier: NCT04274738. Updated May 17, 2022. Accessed September 14, 2022. https://clinicaltrials.gov/ct2/show/NCT04274738.
2. Data on File. X4 Pharmaceuticals, Inc., Boston, MA.

Advanced Clear Cell Renal Cell Carcinoma

Improvements Were Observed in Hematological Parameters With Mavorixafor in Combination With Axitinib

A phase 1/2 trial (NCT02667886) evaluated the safety and tolerability of escalating doses of mavorixafor (200–600 mg QD) in combination with axitinib (5 mg twice daily) in participants with advanced ccRCC who received ≥1 prior therapy[1]

WBC[a] and Differential Leukocyte Counts in Participants With ccRCC Treated With Combination of Mavorixafor and Axitinib (N=63)[2]



- Treatment with mavorixafor in combination with axitinib increased WBC count, ANC, ALC, and AMC to 153%, 158%, 143%, and 182%, respectively, after 4 weeks of treatment, with increases in all parameters sustained at 18 months and in ANC and ALC over 4 years[2]
- Similar results were reported in a study evaluating mavorixafor in combination with nivolumab in metastatic ccRCC (NCT02923531)

ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; ccRCC, clear cell renal cell carcinoma ; WBC, white blood cell.

1. ClinicalTrials.gov. ClinicalTrials.gov identifier: NCT02667886. September 22, 2021. Accessed September 14, 2022. https://clinicaltrials.gov/ct2/show/NCT02667886.
2. Data on File. X4 Pharmaceuticals, Inc., Boston, MA.

Conclusions

Ongoing studies in WHIM syndrome, CNDs, WM, and completed studies in ccRCC show that[1,2]:

- Oral administration of mavorixafor alone or in combination with G-CSF, ibrutinib, or axitinib increased total WBC and all differential leukocyte counts examined over both short-term or long-term treatment across all disease states studied
- Greater treatment effects were observed with WHIM syndrome and CNDs, both characterized by neutropenia at baseline

In the CND trial, rapid increase in ANC was observed regardless of concurrent G-CSF use or type of CNDs[2]

Mavorixafor has been generally well tolerated, with a manageable safety profile across various disease states (WHIM syndrome, CNDs, WM, and ccRCC) either alone or in combination with oncology drugs[1]

These studies support the potential therapeutic use of mavorixafor as the first oral treatment for WHIM syndrome and CNDs

ANC, absolute neutrophil count; ccRCC, clear cell renal cell carcinoma; CNDs, chronic neutropenic disorders; G-CSF, granulocyte-colony stimulating factor; WBC, white blood cell; WHIM, Warts, Hypogammaglobulinemia, Infections, Myelokathexis; WM, Waldenström's macroglobulinemia.

1. Dale C, et al. Oral administration of mavorixafor, a CXCR4 antagonist, increases peripheral white blood cell counts across different states. Oral presentation presented at the 63rd American Society of Hematology Annual Meeting & Exposition; December 11–14, 2021. **2.** Data on File. X4 Pharmaceuticals, Inc., Boston, MA.

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- Axitinib used in ccRCC clinical trial was provided by Pfizer

Thank you!