Understanding Primary Immunodeficiencies

Realizing the Potential of CXCR4 Antagonism

December 16, 2021

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. These statements may be identified by the words “may,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “target,” or other similar terms or expressions that concern X4's expectations, strategy, plans, or intentions. Forward-looking statements include, without limitation, statements regarding the clinical development and therapeutic potential of mavorixafor for the treatment of WHIM syndrome, Waldenström’s macroglobulinemia, congenital neutropenia and other neutropenias and other primary immunodeficiencies, and of X4’s other product candidates; X4’s possible exploration of additional opportunities for mavorixafor; and the expected availability, content and timing of clinical data from X4’s ongoing clinical trials of mavorixafor;.

Any forward-looking statements in this presentation are based on management's current expectations and beliefs. Actual events or results may differ materially from those expressed or implied by any forward-looking statements contained herein, including, without limitation, uncertainties inherent in the initiation and completion of preclinical studies and clinical trials and clinical development; the risk that trials and studies may be delayed, including, but not limited to, as a result of the effects of the ongoing COVID-19 pandemic or delayed patient enrollment, and may not have satisfactory outcomes; the risk that the outcomes of preclinical studies or earlier clinical trials will not be predictive of later clinical trial results; the risk that initial or interim results from a clinical trial may not be predictive of the final results of the trial or the results of future trials; the potential adverse effects arising from the testing or use of mavorixafor or other product candidates; risks related to X4’s ability to raise additional capital; risks related to the substantial doubt about X4’s ability to continue as a going concern; and other risks and uncertainties, including those described in the section entitled “Risk Factors” in X4’s Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 4, 2021, and in other filings X4 makes with the SEC from time to time. X4 undertakes no obligation to update the information contained in this presentation to reflect new events or circumstances, except as required by law.

The Dysregulated Immune System: A Broad Opportunity for CXCR4 Antagonism

Primary Immunodeficiencies
Life-threatening infections & deaths

- >$3.3 billion WW annual Rx sales[1]
- Few options (G-CSF & IVIG)
- Injectable or infusion only

Lymphomas
Cancer progression and deaths

- >$7 billion WW annual Rx sales[2]
- Multiple therapies and multiple lines of treatment
- Few cures

Dysregulation of white blood cells (leukocytes) contributes to a broad range of serious diseases with significantly unmet therapeutic needs

1. Allied Market Research 2019
2. Business Insight, Market Research Report, 2018

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Today's Focus: ASH Data Supporting Broader Therapeutic Potential of Mavorixafor

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Introductions: X4 Management and Thought Leaders on Today's Call

Paula Ragan, Ph.D.
Chief Executive Officer

Diego Cadavid, M.D.
Chief Medical Officer

Art Taveras, Ph.D.
Chief Scientific Officer

Dr. Teresa Tarrant
Allergy & Immunology Specialist, Rheumatology
Duke University

Adam Mostafa
Chief Financial Officer

Dr. Neal Sondheimer
Associate Professor, Dept. of Molecular Genetics and Pediatrics, University of Toronto

Advancing a Pipeline of Oral CXCR4 Antagonists

Candidate	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Expected Milestones	Target Patient Populations
Mavorixafor	**WHIM** (Warts, Hypogammaglobulinemia, Infections and Myelokathexis) syndrome[2]				Phase 3	Top-line data **4Q 2022** **2H 2023 NDA**	**1,000-3,700 U.S.**[3]
	Waldenström's Macroglobulinemia (WM)		Phase 1b			Add'l data / dose selection in **2022**	**2,000-3,000 U.S.**[4]
	Chronic Neutropenia (CN)		Phase 1b			Add'l data in **2022**	**5,000-10,000 U.S.**[5]
X4P-002	Oncology indications	IND-enabling				IND in 2H 2022	Other leukemias and lymphomas >25,000[4]
X4P-003	Primary immuno-deficiencies (PID)						Undisclosed

Potential to address the needs of >30,000[1] patients across multiple indications

1. EU Estimates: using U.S. prevalence. Of each disease and applying it to EU population. 2. Phase 2 open label extension (OLE) trial for WHIM ongoing 3. Company market research. Qessential market research, 2019 and IPM.ai artificial intelligence study, 2020. 4. *WM Epidemiology Analysis Nemetz Group.* Data on file. 5. Estimate using Andersen et al. *J Intern Med.* 2016 Jun;279(6):566-75.

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Primer on Primary Immunodeficiencies - Guest Speaker: Dr. Teresa Tarrant

- A complex disease for patients and clinicians creates significant unmet needs

Mavorixafor: a new potential oral standard of care to address immunodeficiencies

- Broadly increases WBC counts to alleviate cellular deficits and infection risks regardless of mutation status

Mavorixafor and WHIM syndrome

- Fully enrolled global Phase 3 clinical trial; strong Phase 2 data de-risk regulatory pathway
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New Insights on WHIM syndrome – Disease Definition and Prevalence

- A disease spectrum with broader genetic/clinical profiles / larger prevalence than previously understood
- **Guest Speaker: Dr. Neal Sondheimer**
- Expanding patient identification, physician and patient support and market access efforts

Mavorixafor and Chronic Neutropenia (CN)

- CN has high unmet need; SoC is limited and has known risks
- Promising initial Phase 1b data in CN signals expanding role for mavorixafor in additional immunodeficiencies

Fireside Chat with Dr. Tarrant – the Physician Perspective

Wrap-Up / Q&A

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What are Primary Immunodeficiency Diseases (PIDs)?

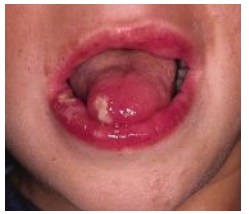
- A group of more than **>400 rare, chronic conditions** in which part of the body's immune system is missing or does not function correctly.
- PIDs can be **hereditary genetic defects** that can affect anyone, regardless of age, gender, or ethnicity, or can be idiopathic.
- Most often characterized by
  - **Chronic, debilitating infections** - pneumonia, bronchitis, sinus infections, ear infections, meningitis or skin infections – severe, persistent, unusual, recurrent, may run in the family
  - **May Increase the risk of developing cancer**
  - Inflammation and infection of internal organs
  - Blood disorders – anemia, neutropenia, lymphopenia, antibody deficiency
  - Digestive problems, such as cramping, loss of appetite, nausea and diarrhea
  - Delayed growth and development
  - Autoimmune disorders, such as lupus, rheumatoid arthritis or type 1 diabetes
- May be **diagnosed in infancy, childhood, or adulthood**, depending on disease severity
- **~250,000 people diagnosed with PIDs and thousands more undetected in the U.S.**

Source: Immune Deficiency Foundation *https://primaryimmune.org/*

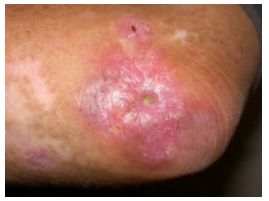
Challenges in Diagnosing PIDs

- **Signs and symptoms differ** depending on the type of primary immunodeficiency disorder, and they vary from person to person
- **THINK ZEBRA!** In medical school, doctors learn the saying, "when you hear hoof beats, think horses, not zebras," and are taught to focus on the likeliest possibilities when making a diagnosis, not the unusual ones
  - **Patients with primary immunodeficiency diseases can be zebras in the medical world**
- **Early diagnosis of PI is critical:**
  - Average time from symptom onset to diagnosis is between 9 and 15 years per the Immune Deficiency Foundation (IDF)
  - During this gap, 37% of patients report permanent functional impairment, including lung disease (per IDF)
  - With earlier diagnosis, many of these permanent impairments could be avoided

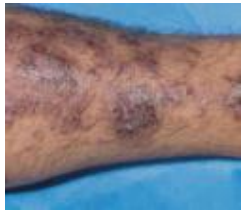
Immunodeficiencies (US Prevalence)



Chronic Neutropenias[2]
5,000 - 10,000
(severe and moderate)



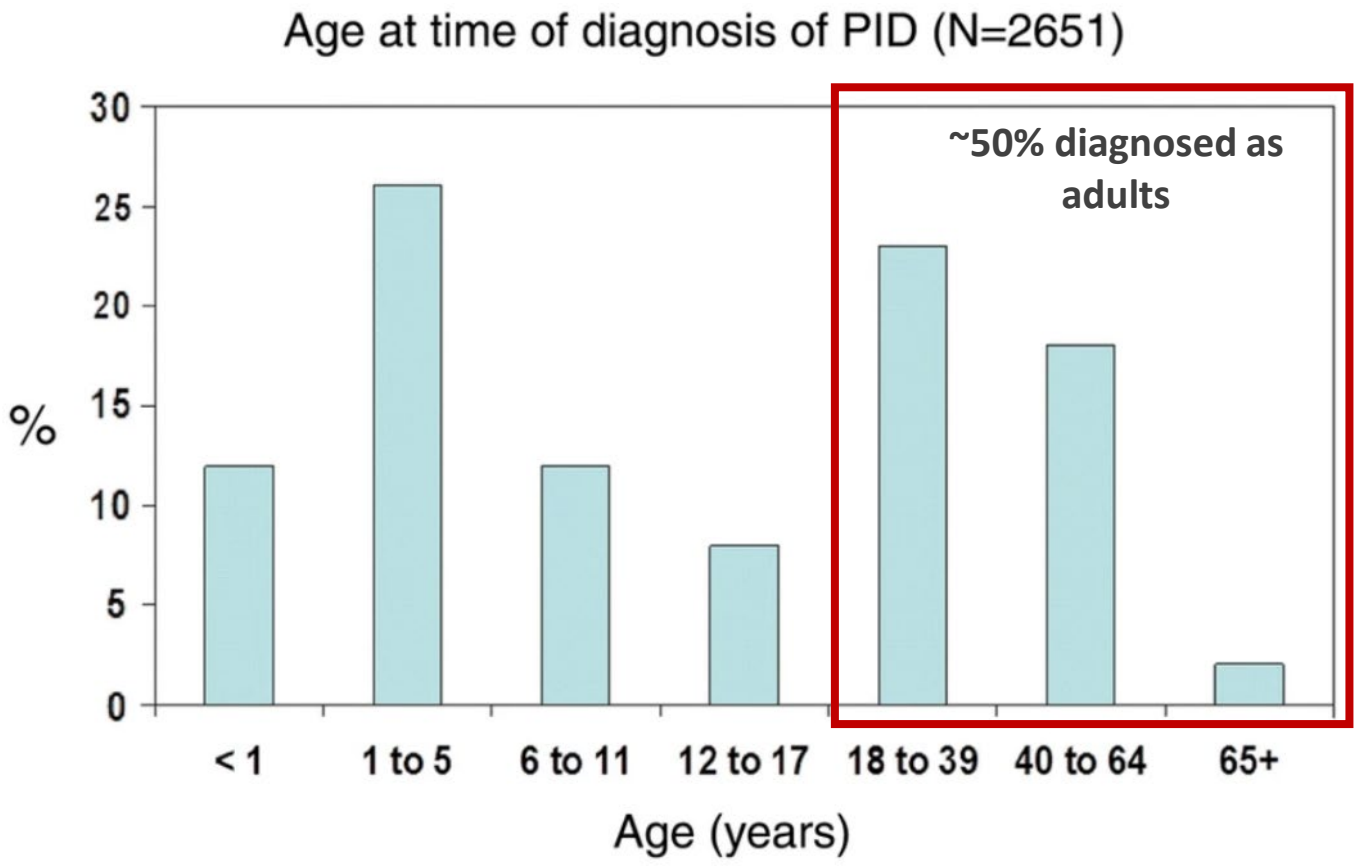
Common Variable Immunodeficiency (CVID)[1]
>10,000



WHIM Syndrome[3]
~1,000 to 3,700

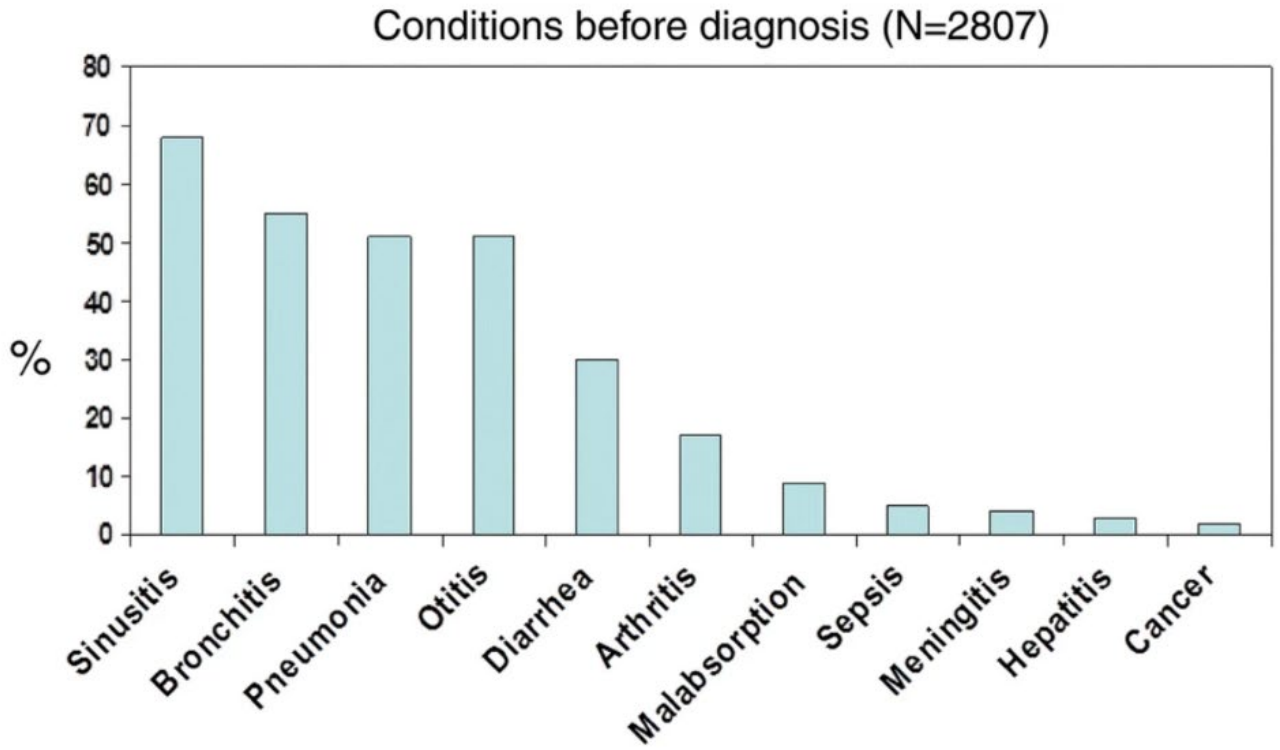
1. Odnoletkova et al *Orphanet Journal of Rare Diseases* v1**3**, 201 (2018) 2. US estimate for severe plus 10% penetrance for moderate and prevalence from Andersen et al. *J Intern Med.* 2016 Jun;279(6):566-75. 3. Company market research. Qessential market research, 2019 and IPM.ai artificial intelligence study, 2020

Majority of PID Patients Diagnosed as Adults



McCusker, C., Upton, J. & Warrington, R. Primary immunodeficiency. *Allergy Asthma Clin Immunol* **14,** 61 (2018). https://doi.org/10.1186/s13223-018-0290-5

Common Conditions Experienced by People with PIDs



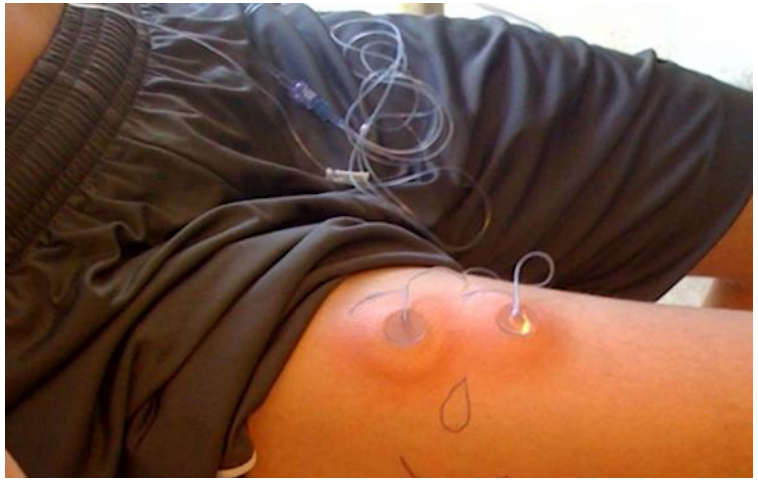
Significant increases in lymphoma in both men (10-fold increase, $P < .001$) and women (8.34-fold increase, $P < .001$) with PID observed

McCusker, C., Upton, J. & Warrington, R. Primary immunodeficiency. *Allergy Asthma Clin Immunol* **14,** 61 (2018). https://doi.org/10.1186/s13223-018-0290-5

Journal of Allergy and Clinical Immunology Volume 141, Issue 3, March 2018, Pages 1028-1035

Treatment & Management: Limited Options for Chronic Disease

- Replacement Strategies
  - IVIG for antibody deficiency and G-CSF for neutropenia
  - Bone marrow transplant
- Immune Modulation
  - High dose IVIG
  - Anti-inflammatories
- Broad Immunosuppression
  - Corticosteroids
  - Steroid-sparing agents (e.g. azathioprine, mycophenolate mofetil)
  - mTOR inhibitors (e.g. sirolimus)
  - Biologics and small molecule inhibitors (e.g. TNF inhibitors)
- Hematopoietic Stem Cell Therapy
- Gene Therapy specific to disease type

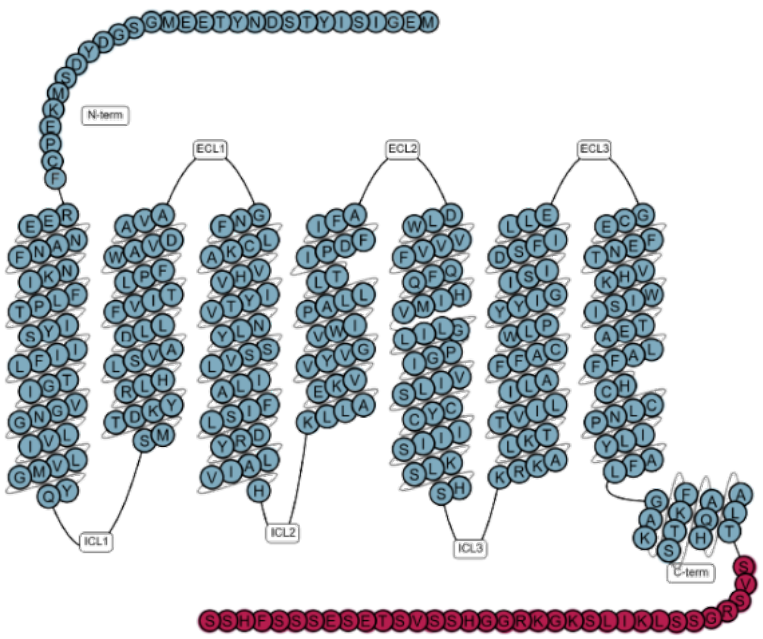


ADAPTED FROM:
IDF's Rare of the Rare session, "Precision Medicine Targeted Therapy for Primary Immunodeficiency: Where Are We Now?" was presented by Jennifer Leiding, MD, Lisa Forbes Satter, MD, and Caroline Kuo, MD on October 1, 2021.

Root Cause of WHIM Syndrome: Over-Signaling of CXCR4 due to Genetic Mutations

Gain-of-Function mutations cause over-signaling

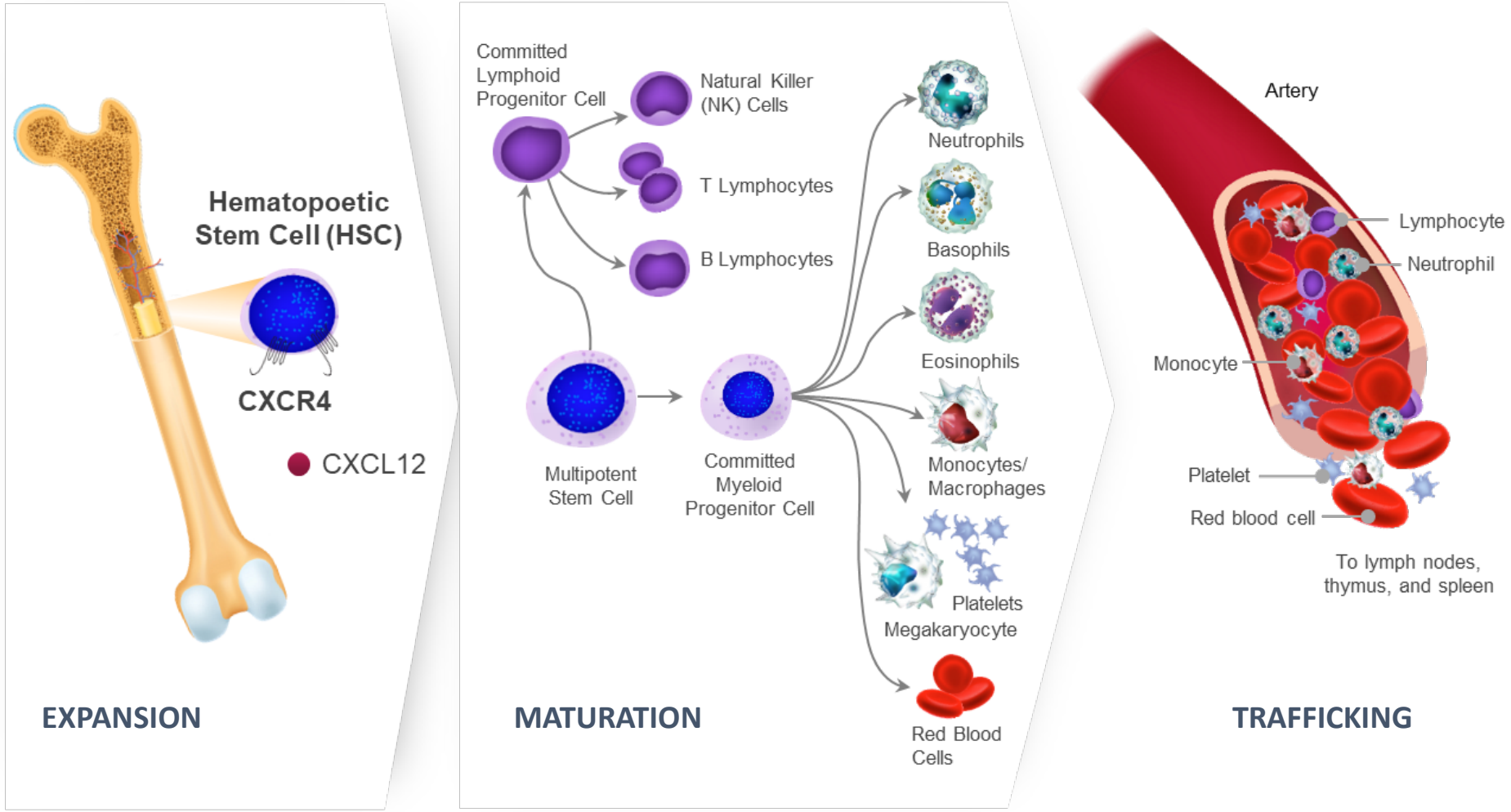
CXCR4 Receptor



Impacting immune cell expansion, maturation, and trafficking

- **WHIM Syndrome:** spectrum of clinical presentations mostly with (and sometimes without) CXCR4 mutations
  - **W**: warts
  - **H**: hypogammaglobulinemia
  - **I**: infections
  - **M**: myelokathexis (hyper-cellular bone marrow)
- In most cases, **autosomal dominant disease** driven by pathogenic CXCR4 mutations; mostly located in "tail" (c-terminus) of receptor
  - ~16 in the literature to date; # increasing with research
- Results in **over-signaling of CXCR4 impacting all white blood cells**

CXCR4/CXCL12 Pathway: Master Regulator of Immune System Function



Inhibition of the CXCR4/CXCL12 pathway creates the potential for therapeutic benefit across a wide rage of diseases with significant unmet needs

In Summary

- **Large number of PIDs**, which can be of genetic origin or idiopathic
  - Estimated 250,000 U.S. population, plus more undiagnosed

- **PIDs are heterogeneous and can be difficult to diagnose** due to
  - Variability of patient presentation
  - Lack of understanding amongst the general physician community

- **Early diagnosis (plus treatment, if available) is key** to preventing long-term serious complications and cancer

- **Current treatment options are limited** and do not address patients' chronic needs

- **The CXCR4/CXCL12 pathway presents a logical mechanism to address neutropenia and potentially other cellular immunodeficiencies through CXCR4 antagonism**

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Mavorixafor: CXCR4 Antagonism in a Capsule

Addressing the unmet need in immunodeficiencies: Oral treatment with the potential to correct and regulate a range of immune system deficiencies

The only oral CXCR4 antagonist in clinical development

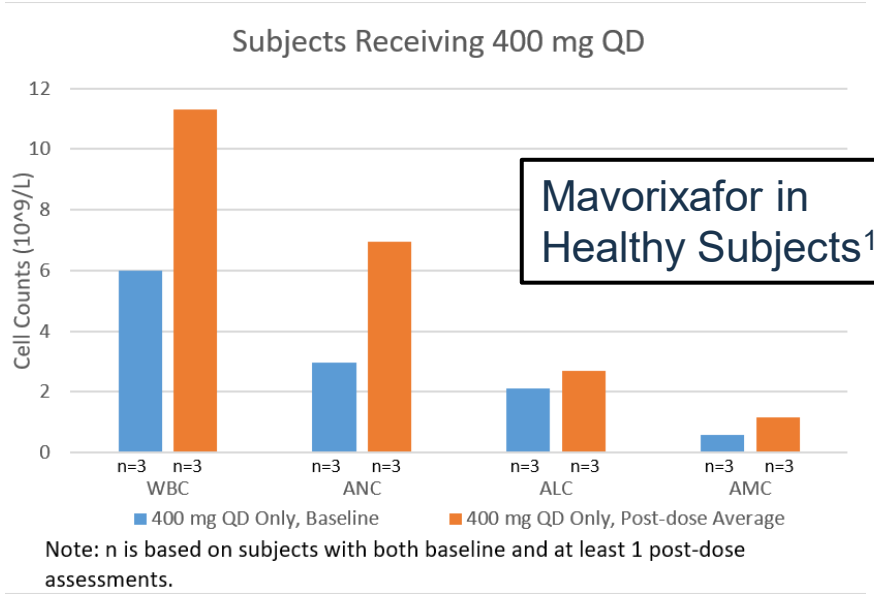
- Small molecule with high potency and selectivity
- Durable half-life supporting once daily dosing
  - Dose: 2 or 4 100 mg capsules taken once daily (WHIM)

Safety profile supports chronic administration

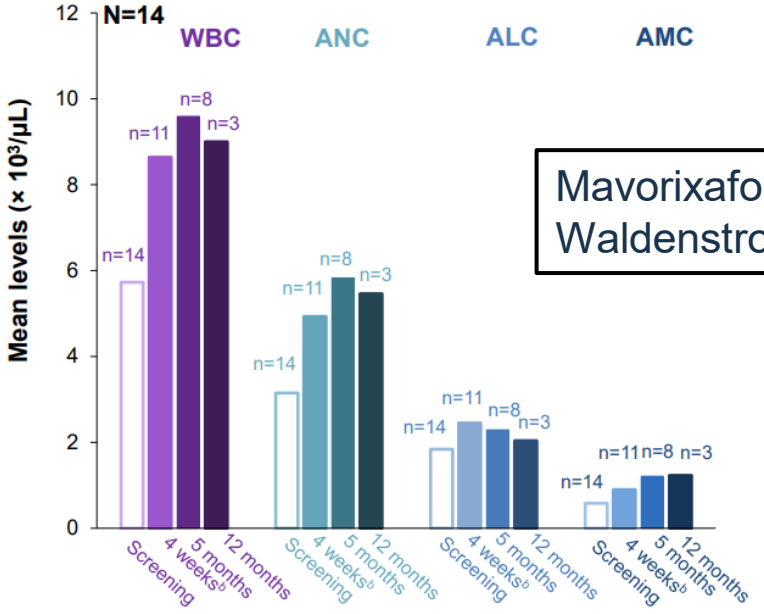
- > 200 patients/subjects treated to date
- Multiple patients on treatment for several years

Patent protection anticipated through at least 2038

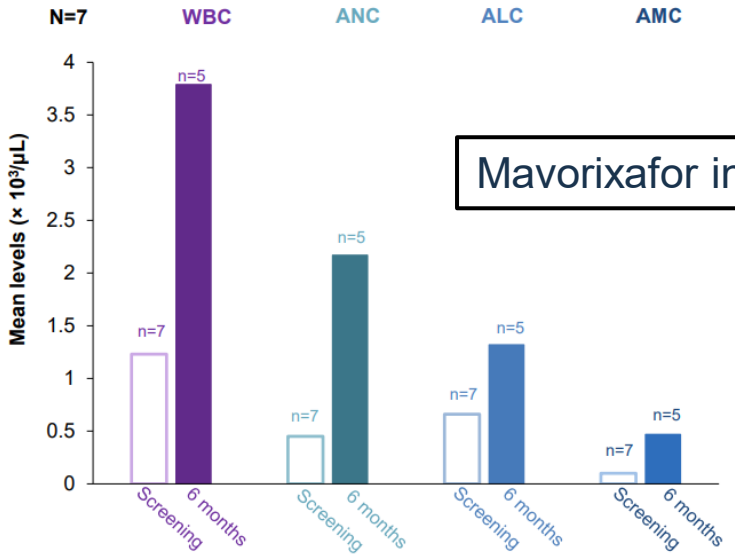
ASH 2021: Mavorixafor: The First Oral Treatment to Increase Peripheral White Blood Cell Counts Across Diverse Disease States



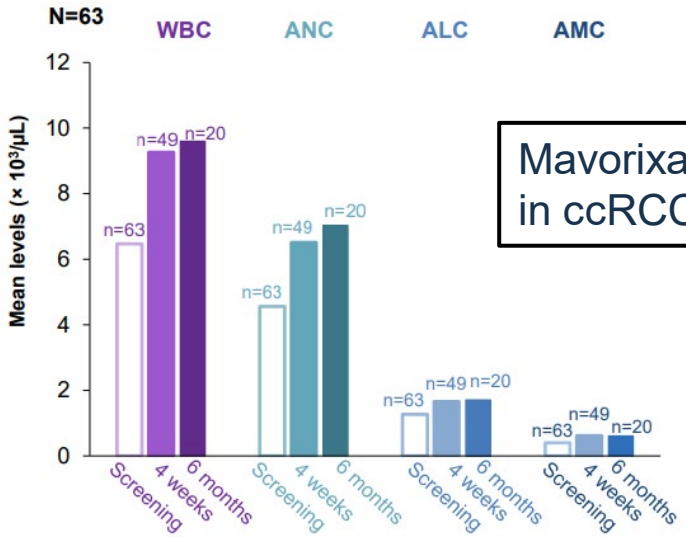
Mavorixafor in Healthy Subjects[1]



Mavorixafor + Ibrutinib in Waldenstrom's Macroglobulinemia



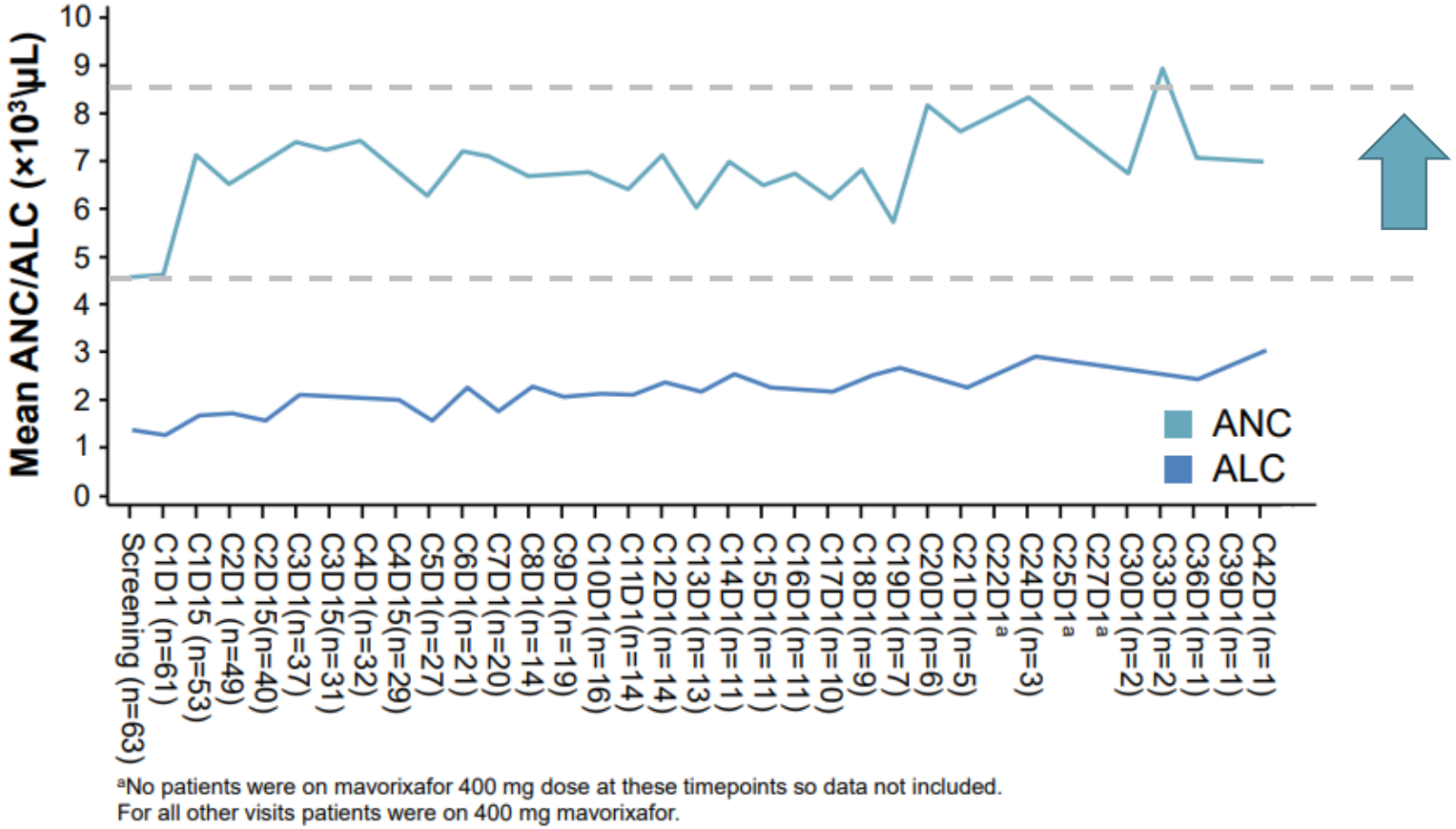
Mavorixafor in WHIM



Mavorixafor + Axitinib in ccRCC

ASH 2021: Mavorixafor Safely and Durably Increases Neutrophils and Lymphocytes Over Years of Treatment

Phase 2a Trial - RCC Patients Chronically Treated with 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.

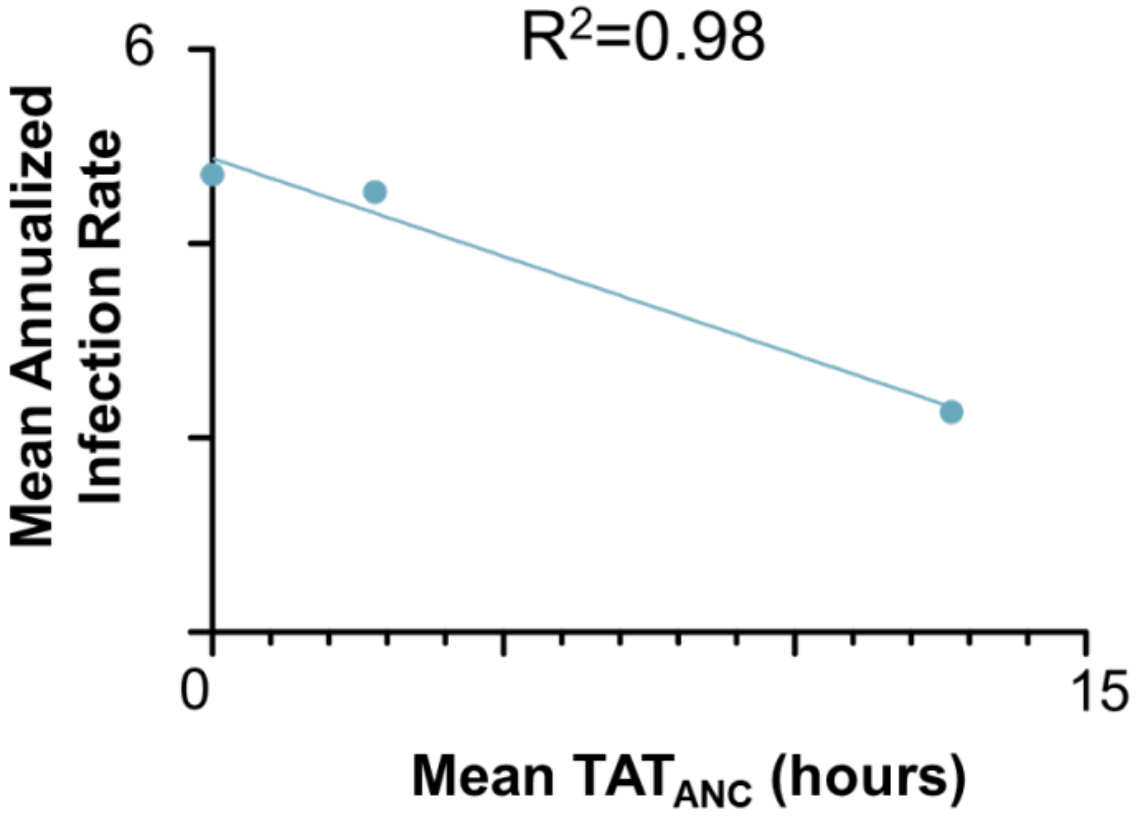
Neutrophil counts (ANC) increase beginning after oral dosing with ~2-fold increase observed

Elevations sustained over multiple years

Similar impact also observed in lymphocytes (ALC)

* Axitinib, an anti-angiogenic treatment approved for kidney cancer, does not increase neutrophil, lymphocyte or other WBC counts.

ASH 2021: Infection Risk Reduced with Mavorixafor: Phase 2 WHIM Study

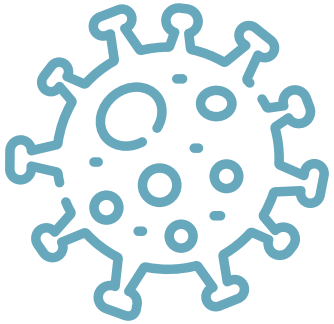


- **Prior studies correlate low neutrophil counts with increased infection risk**
- **WHIM Phase 2 study demonstrated mavorixafor reduced infection risk with elevated neutrophil counts (TAT_{ANC})**

Datapoints (L to R) correspond to dose levels:
pre-treatment, low dose (50-150mg), and high dose (300/400mg) mavorixafor

Mavorixafor: Potential to Become SoC Across a Range of Immunodeficiencies

- Mavorixafor broadly increases total peripheral WBCs and all WBC subsets
  - Regardless of the presence or absence of CXCR4 gain-of-function mutations
  - Alone or in combination with other treatments
  - Across a range of disease settings
- Increases in WBC counts occurred rapidly and were sustained during chronic treatment
- Reduction of cytopenias with mavorixafor translates into a reduced infection burden as demonstrated by initial evidence in WHIM Phase 2, and supported by correlation between chronic cytopenias and increased serious/severe infections



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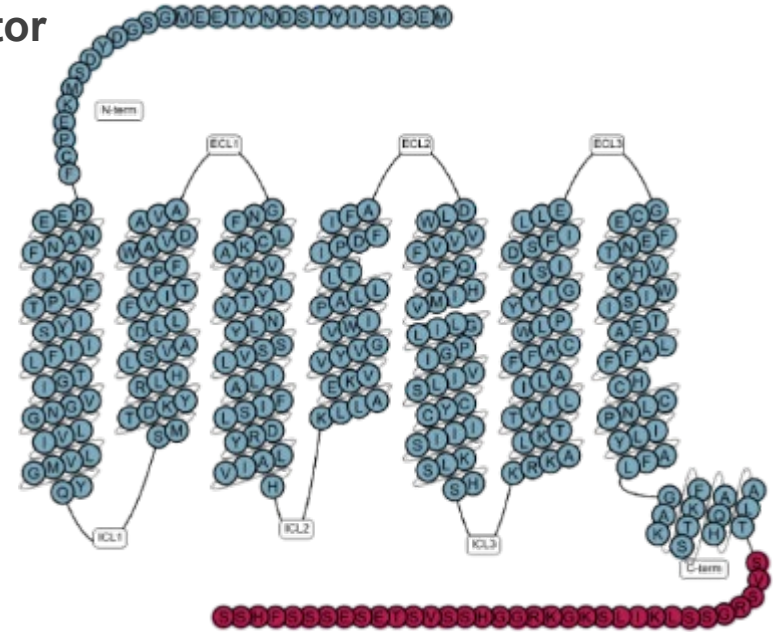
  - **W** warts
  - **H** hypogammaglobulinemia
  - **I** infections
  - **M** myelokathexis (hyper-cellular bone marrow)
- In most published cases, **autosomal dominant disease** driven by pathogenic CXCR4 mutations; mostly located in "tail" (c-terminus) of receptor
- WBCs get stuck in the bone marrow rather than egress to the periphery to help prevent and fight infections
- Can be diagnosed **<u>with or without</u> CXCR4 mutations**

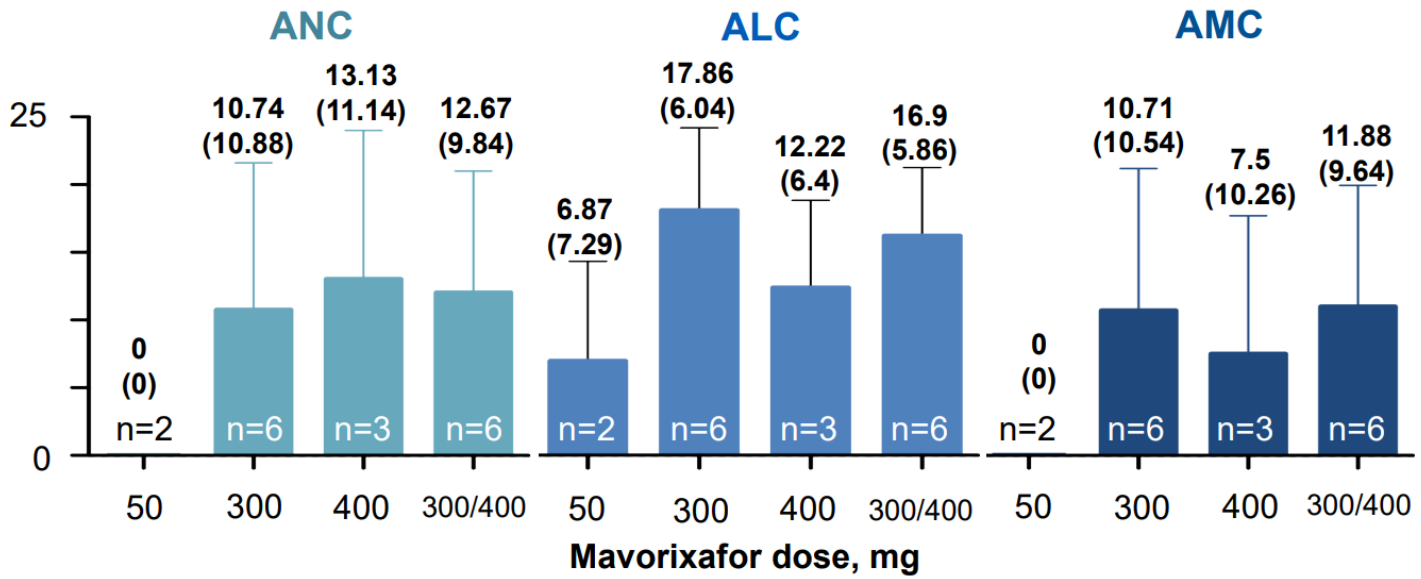
CXCR4 receptor



In most patients, CXCR4 over-signaling **<u>negatively impacts</u>** the development, maturation, and trafficking of immune cells within the bone marrow

ASH 2021: Mavorixafor in WHIM Syndrome: Phase 2 Study Shows Continued Benefit

Mean Time Above Threshold (TAT, hours) for ANC, ALC, and AMC



- **Patient interviews** revealed long-term treatment with mavorixafor to be well tolerated and continuing to demonstrate beneficial treatment effects, including:
  - decreased frequency, severity, and duration of infections and
  - fewer hospital/doctor visits.

- **Decreases in mean annualized infection rates correlate well with TAT_{ANC}, the primary endpoint in our ongoing, fully enrolled, global, Phase 3 registrational trial**

- Data continue to support the potential of mavorixafor to be a safe, effective, and long-term oral therapy targeting the underlying cause of WHIM syndrome

Phase 3 top-line clinical results expected in 4Q 2022

Clear and Favorable Regulatory Pathway for Mavorixafor in WHIM

WHIM Regulatory Designations Granted by the FDA

- ✓ Breakthrough Therapy
- ✓ Fast Track
- ✓ Rare Pediatric Disease (PRV eligible)
- ✓ Orphan Drug

Ph 3 Registrational Study Fully Enrolled (as of Oct '21)

- ✓ Randomized Placebo-Controlled Double-Blinded Design
- ✓ Exceeded enrollment (31 patients)
- ✓ >50% are adolescents (12-17 yrs) supporting RPD designation
- • *Pending*: Topline data in Q4 2022

Mavorixafor Potential Label

- • *Pending:* for the treatment of WHIM syndrome in patients ≥ 12 years
- ✓ *No companion diagnostic (genetic testing) is likely to be required*

Understanding the Definition and Diagnosis of WHIM Syndrome

Mavorixafor Potential Label

For the treatment of WHIM syndrome in patients ≥ 12 years

Diagnosis of WHIM Syndrome:

Combined Immunodeficiency[1] w/ clinical presentation

1. **Pathogenic / likely pathogenic CXCR4 mutations**
2. **Confirmed Myelokathexis**
3. **Novel genes/mutations** impacting WBC maturation & trafficking – *but no CXCR4 mutations*[2]

The Different Faces of WHIM

1. **"Combined Immunodeficiency"** is defined as one or more of abnormal neutrophils (ANC) lymphocytes (ALC) and monocytes (AMC) and hypogammaglobulinemia. Clinical presentation of infections (bacterial and/or viral including HPV) is also required.

2. WHIM syndrome has been diagnosed without CXCR4 mutations or myelokathexis. *Heusinkveld LE, Yim E, Yang A, Azani AB, Liu Q, Gao JL, McDermott DH, Murphy PM. Pathogenesis, diagnosis and therapeutic strategies in WHIM syndrome immunodeficiency. Expert Opin Orphan Drugs. 2017;5(10):813-825. doi: 10.1080/21678707.2017.1375403. Epub 2017 Sep 25. PMID: 29057173; PMCID: PMC5648064.*

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Building the Market: Genotype/Phenotype Research and Patient Identification

Phase 3 Patient Screening

PATH4WARD
Patient Access To Hope
for Rare Primary Immunodeficiencies

Physician Inquiry

X4's Field Force (MSL/PDL) Efforts

Diagnosis of WHIM Syndrome:

Combined Immunodeficiency[1] w/ clinical presentation

and one or more of the following

Today's Focus: Genotype/Phenotype

1. **Pathogenic / likely pathogenic CXCR4 mutations**
2. **Confirmed Myelokathexis**
3. **Novel genes/mutations** impacting WBC maturation & trafficking – *but no CXCR4 mutations*[2]

Known variants

Unknown variants

Newly identified variants

ASH 2021: Novel WHIM-Causing CXCR4 Variant Found / D84H Case Study

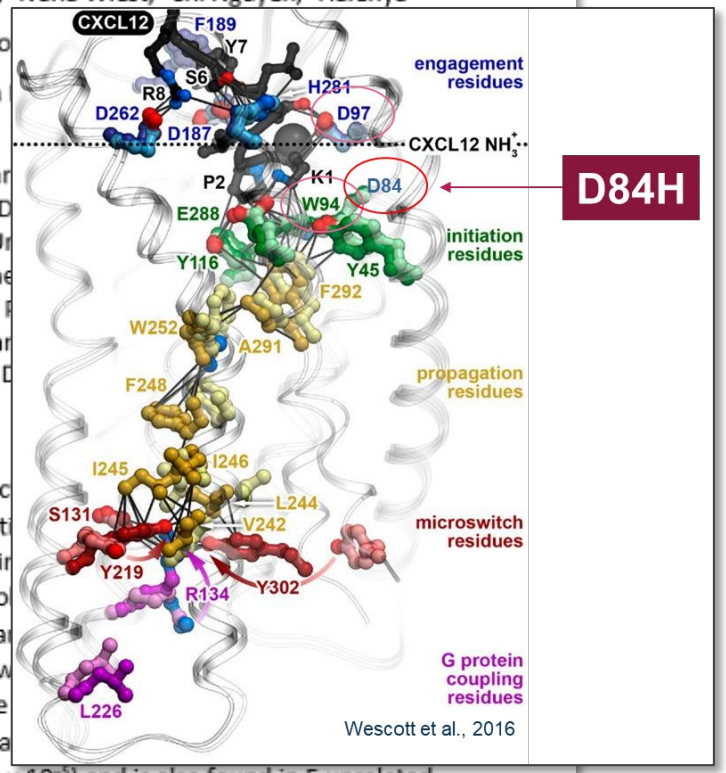
- First report of a missense mutation in CXCR4 outside of the C-terminus causing a WHIM phenotype
- Highlights defective chemotaxis in NKT cells, which may be relevant in HPV-associated carcinoma
- Based on analysis of population databases, conservative estimates predict there to be potentially ~2,500 individuals in the U.S. with disease due to the D84H variant alone
- Further highlights under-recognition of WHIM syndrome

Characterization of a Novel Missense *CXCR4* Mutation in a Patient With WHIM-like Syndrome

Sumit Pawar,[1] Katarina Zmajkovicova,[1] Svetlana Sharapova,[2] Ivana Wiest,[1] Chi Nguyen,[1] Halenya Monticelli,[1] Sabine Maier-Munsa,[1] Christoph Geier,[3] Neal So
Marryssa Ellison[5], Jolan Walter,[5] Arthur G. Taveras,[6] Adriana

[1]X4 Pharmaceuticals (Austria) GmbH, Vienna, Austria; [2]Belar
Oncology, Hematology, and Immunology, Minsk, Belarus; [3]D
Immunology, Center for Chronic Immunodeficiency (CCI), U
Germany; [4]Division of Clinical and Biochemical Genetics, The
Canada; [5]Division of Allergy & Immunology, Department of
University of South Florida, St Petersburg, FL, USA; [6]X4 Phar
Rheumatology and Immunology, Department of Medicine,
of X4 Pharmaceuticals

Background: WHIM (Warts, Hypogammaglobulinemia, Infec
primary immunodeficiency with a heterogeneous presentat
well as panleukopenia. The majority of cases are inherited i
of-function mutations in the C-terminus of the C-X-C chemo
Immunol Rev. 2019;287:91-102). To our knowledge, there a
CXCR4^{WHIM} mutations outside the CXCR4 C-terminus. Here w
patient with the novel mutation *CXCR4*^{D84H} and characterize
CXCR4 trafficking and chemotaxis in *in vitro* and *ex vivo* assa
population genetic databases (average allele frequency 3.8×10^{-5}) and is also found in 5 unrelated patients in another rare disease database (CentoMD).



First D84H Patient Identified: Expanding Phenotype/Genotype of WHIM Syndrome

	P-D84H	Normal range
Age, y	41	
Sex	female	
Skin warts	+	
Genital warts	+	
IgG, mg/dL	1060	588-1573
IgA, mg/dL	94	45-287
IgM, mg/dL	109	57-237
IgE, mg/dL	16	4-269
WBCs, $x10^9$/L	2.2	4.5-11
Neutrophils, $x10^9$/L	0.59	1.63-7.55
Lymphocytes, $x10^9$/L	1.5	0.97-3.96
Bone marrow biopsy	bilobed neutrophils and granulocyte precursors	
Recurrent bacterial infections	-	
Susceptibility to HPV	+	

- 40-year-old female with recurrent vulvovaginal and anal dysplasia
- Carcinoma requiring multiple surgeries from age 20
- Cytopenia since age 15 with mononucleosis
- Decreased neutrophil and WBC counts and normal hemoglobin
- Bone marrow biopsy revealed bilobed neutrophils and granulocyte precursors
- No history of infections beyond HPV/EBV
- No family history of warts, immunodeficiency, or squamous cell carcinoma

Additional D84H Patients Identified in Clinics and in Databases

Clinical Presentation

Patient 1: 12-year-old male

- Low platelets and WBCs, **multilineage cytopenia**, **increased cellularity in bone marrow,** herpetic stomatitis and lesion in oral cavity
  - May 2020: COVID-19, blood transfusions
  - June 2020: lung edema, bilateral hydrothorax, hydropericarditis, ascites, polyserositis
  - July 2020: multinodular toxic goiter, hyperthyreosis, autoimmune thyroiditis
  - Sept 2020: **lung bleeding, bilateral pneumonia, mucormycosis in lung**
  - Sept 2021: **COVID-19 re-infection**

Patient 2: 3-year-old male (deceased)

- Hemorrhagic rash and **low platelets**: 1.8 – 73.3 x10^9/L; WBC 4.7-13 x10^9/L
- Patient died due to bleeding at 4 yrs

Databases (ClinVar, CentoMD)

Patient 1: Female, 67 yrs

- **Variable Immunodeficiency** /antibody deficiency

Patient 2: Female, 41 yrs

- Hypertension; **Thrombocytopenia**; Anemia; Micro-angiopathic hemolytic anemia; Migraine; Preeclampsia

Patient 3: Female, 33 yrs

- No information

Patient 4: Female, 6 yrs 11 mos

- **Thrombocytopenia**; Abnormal bleeding; Anemia

Patient 5: Female, 6 yrs 9 mos

- Hepatosplenomegaly; **Thrombocytopenia**; Abnormal bleeding; Anemia

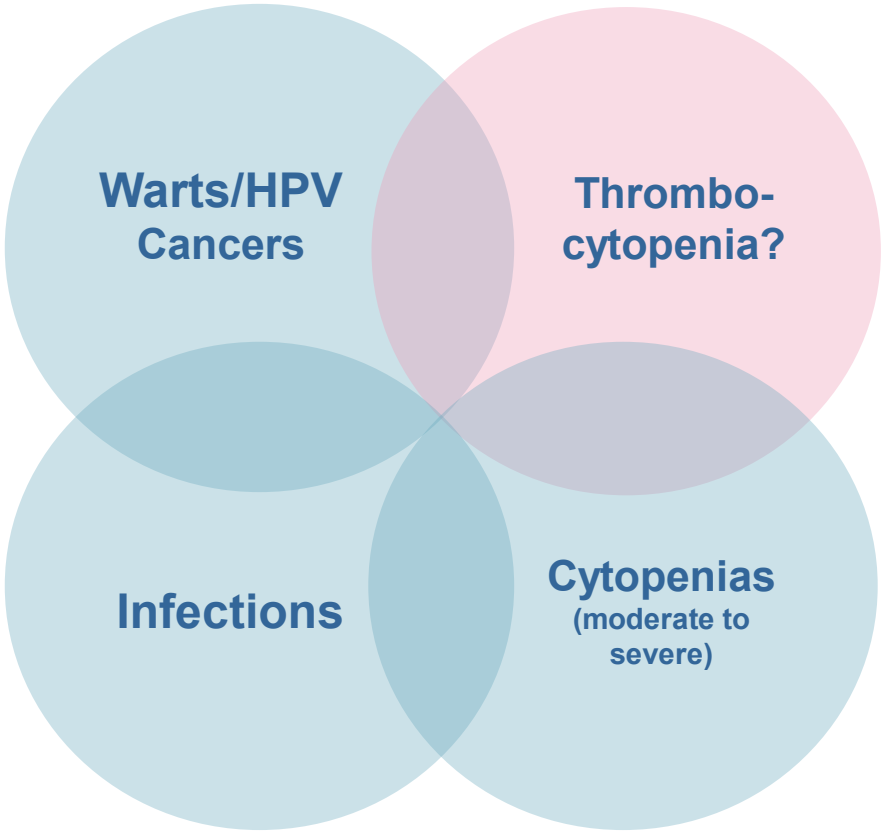
Patient 6: Female, 11 mos

- High palate; Microcephaly; Global developmental delay; Motor delay; Hypertonia; Increased serum lactate; Prominent metopic ridge; Many other

Additional research and outreach ongoing to verify and understand patient profiles

Expanding WHIM Phenotype Associated with D84H Genotype

Multiple Patients In Multiple Regions and From Unique Families



Classic WHIM Symptoms

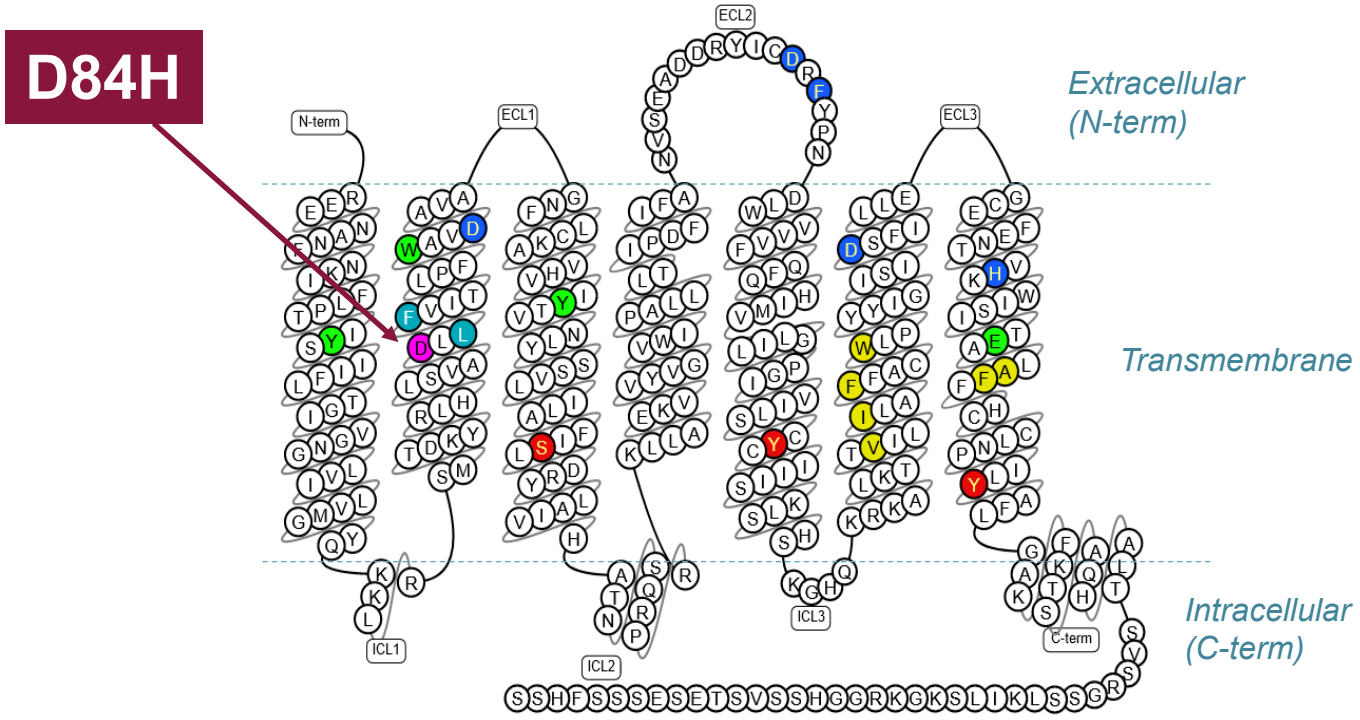
- ✓ HPV warts and/or cancer
- ✓ Infections
- ~ Cytopenias – ***variable: moderate to severe***

❖ NEW Phenotypic Characteristic To Assess:
Thrombocytopenia (low platelets)

Is there a new profile to add: WHIM-T?

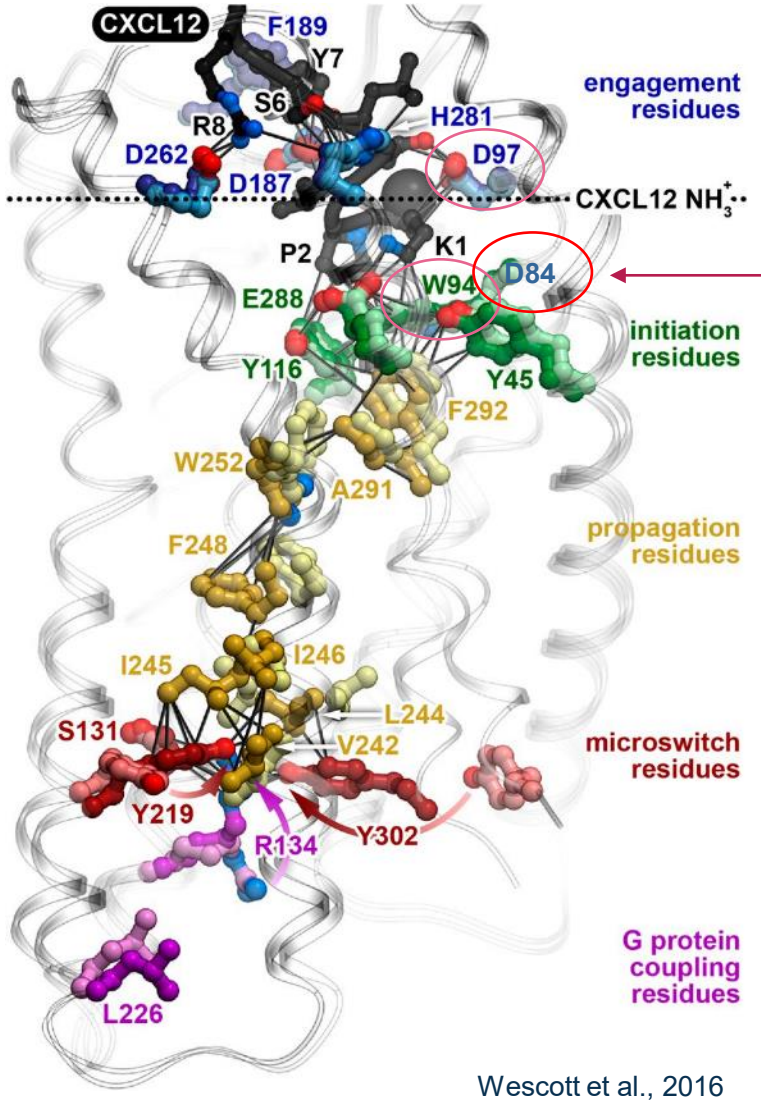
D84H Case Study: First-of-its-Kind Mutation Located Outside C-Terminus

Amino Acid Sequence of GPCR CXCR4



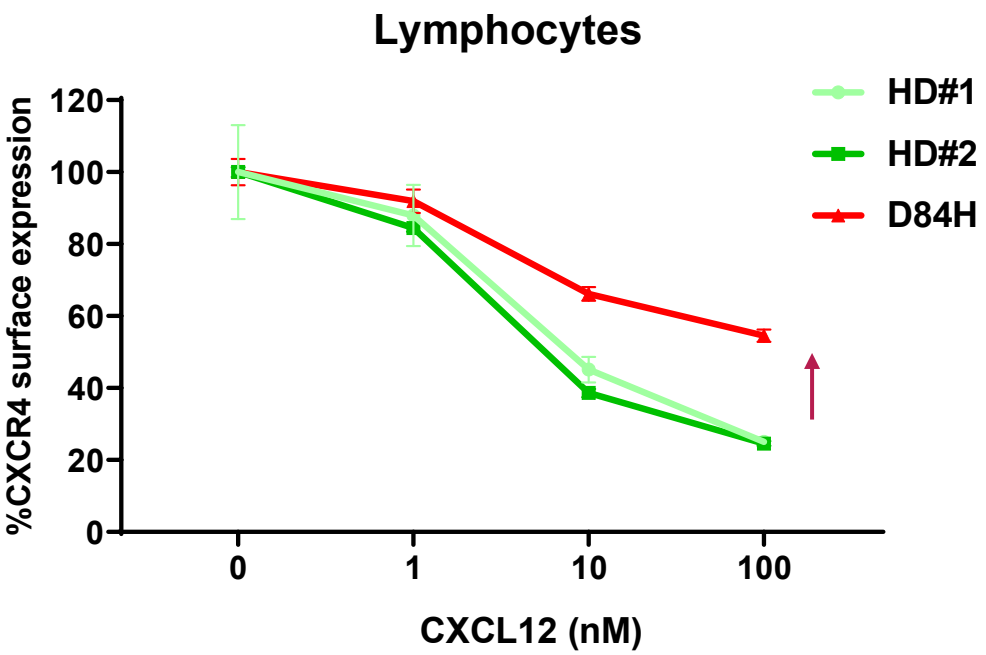
D84 residue is localized in the second transmembrane region, near residues involved in ligand recognition and signal initiation and far from the WHIM “hotspot” (C-terminus)

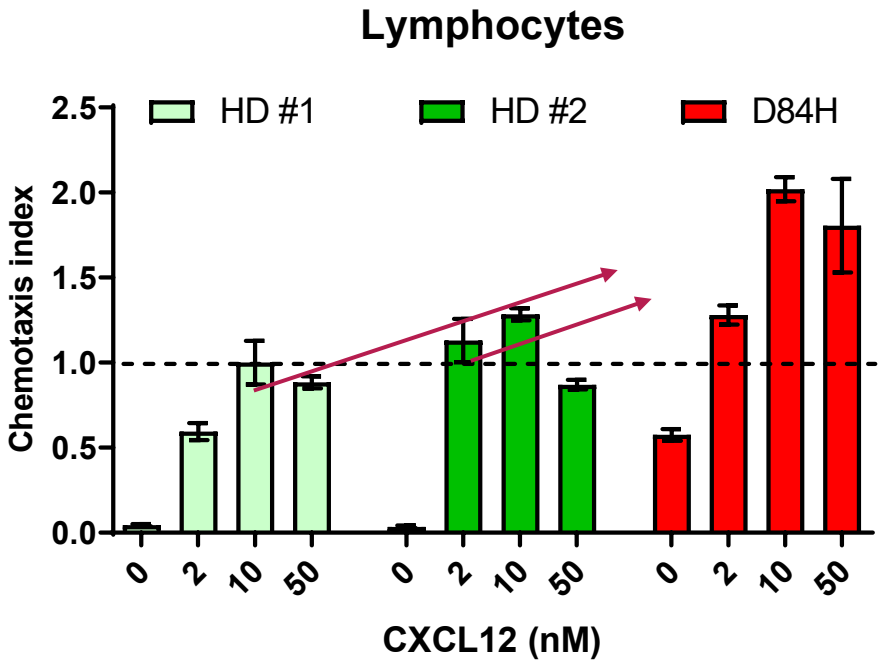
X-Ray Crystal Structure of CXCR4



Wescott et al., 2016

D84H Case Study: Lymphocytes from Patient Harboring CXCR4^{D84H} Showed Defects in CXCR4 Internalization and Chemotaxis

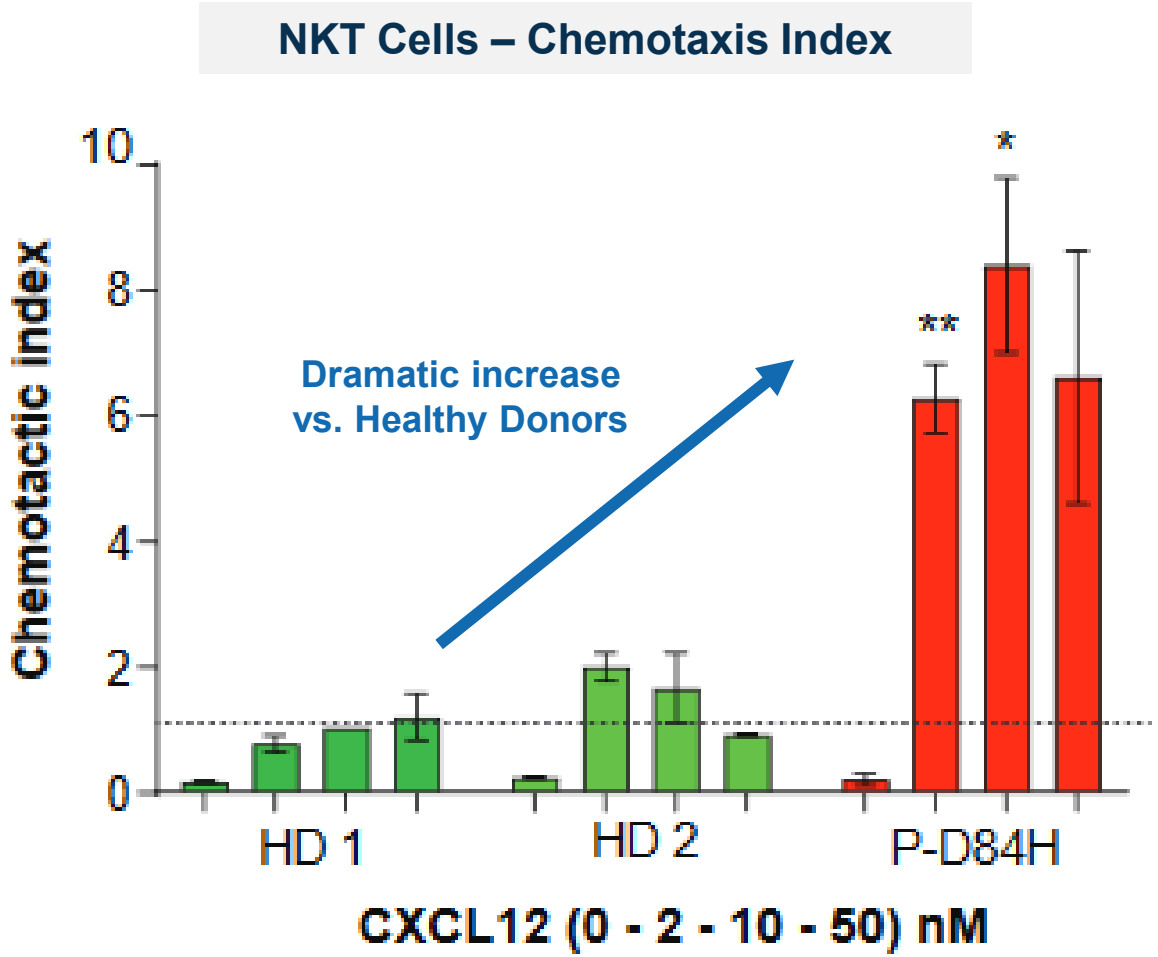




D84H: Patient carrying CXCR4^{D84H} mutation
HD#1: Heathy donor age/ gender matched
HD#2: Healthy donor (Red Cross, Vienna)

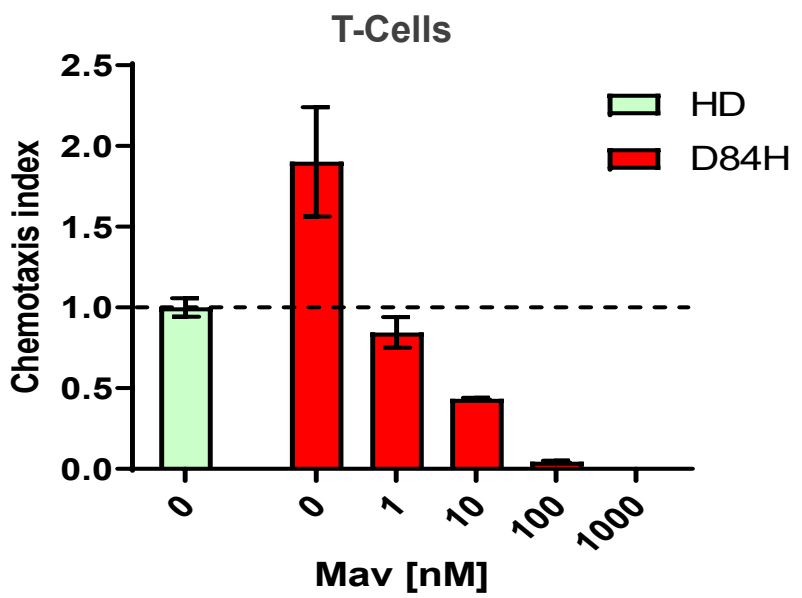
Ex vivo assays with patient samples indicate that CXCR4^{D84H} recapitulates phenotypic defects of known WHIM variants and confirm the findings of X4's *in vitro* screening approach

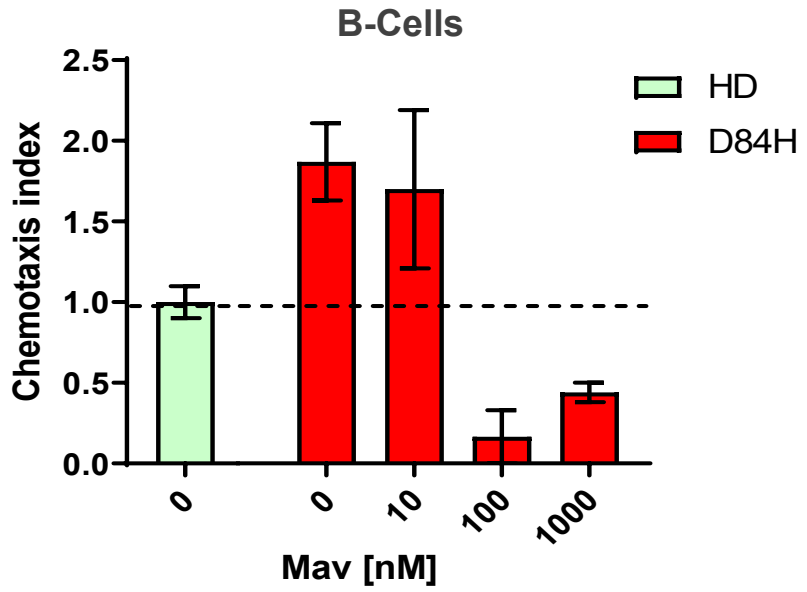
Natural Killer T-Cells (NKT), Associated with Cervical Cancer Prognosis, Have Altered Profiles in D84H Patients vs. Healthy Donors



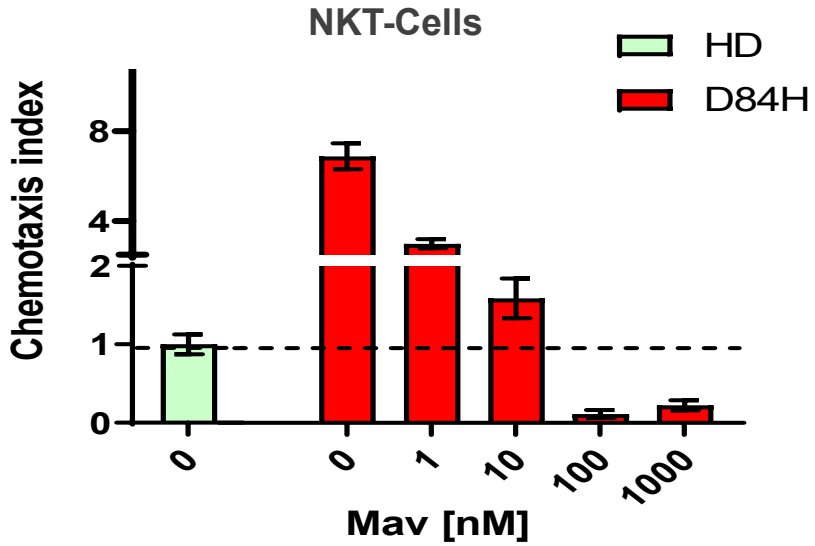
Differences seen in NKT Cells support published findings that associate NKT cell tumor infiltration with Cervical Cancer progression via increased NKT chemotaxis within the tumor

D84H Case Study: Mutation is Sensitive *in vitro* to Mavorixafor





PBMCs isolated from D84 Patient



Mavorixafor inhibits CXCL12-dependent chemotaxis of PBMC subpopulations

Guest Speaker: Dr. Neal Sondheimer

Associate Professor, Dept. of Molecular Genetics and Pediatrics, University of Toronto

Estimating Rare Disease Prevalence Through Use of Publicly Available Databases

NEAL SONDHEIMER M.D., PH.D. – BACKGROUND

- M.D. with training in pediatrics, clinical and metabolic genetics
  - Section Head for Metabolic Genetics, HSC - Toronto
  - Associate Professor of Molecular Genetics – University of Toronto

- Research areas
  - Rare disease discovery
  - Use of large genotype data sets for GWAS, phenotype prediction and risk assessment

- Consulting activities
  - Use of publicly available data sets for estimating disease prevalence

DETERMINING PREVALENCE OF AN ALLELE

- We used large, publicly available genotype databases to identify allele frequency.
  - **gnomAD** – 140K individuals without severe disease. Data set reflective of US population ethnicity, skews slightly older, modest over-representation of males
  - **TopMed** – 150K individuals compiled from multiple population studies. No specific exclusion of disease. No age statistics, but most studies are adult. African-Americans are over-represented
  - **NHLBI Exome Sequencing Project (ESP)** – 200K individuals compiled from multiple studies, largely of cardiovascular phenotype. Population is biased towards adults
- We are looking for concordance of the estimates of any given allele.
- As databases grow, merge and improve these estimates gain confidence over time.

Dataset	Allele frequency p.D84H
gnomAD	$2.8x10^{-5}$
TopMed	$7.7x10^{-5}$
ESP	$7.6x10^{-6}$
Average	$3.8x10^{-5}$

To Convert to Affected Numbers
- Allele Frequency * 2 * population
- For U.S. ~25,000 individuals

ESTIMATING PENETRANCE FOR DOMINANT DISORDERS

- D84H is not 100% penetrant for WHIMS.
  - The allele frequency is higher than C-terminal truncating alleles ($\sim 10^{-8}$) but was not a disease-defining.
  - Common in rare disease studies to find full penetrance, rare mutations first.
- D84H does cause disease…so how many patients does this allele add?
- Penetrance refers to the percentage of individuals with a given genotype who have the phenotype.
  - For p.D84H, what matters is what percentage of individuals are treatable, rather than the percentage that have the complete WHIMS phenotype.
- Conservative estimate of 5-10% treatable has been applied
  - ~1,250-2,500 patients in the U.S.

IMPROVING PENETRANCE ESTIMATION

- Family studies – genotyped kindreds allow us to look at three features
  - Direct calculation of penetrance – How many genotyped individuals currently manifest a phenotype. This is less useful than it appears for diseases with delayed onset and the estimate is less powerful with small numbers.
  - Two other factors can be used to refine a penetrance estimate using the assumption that the incidence of disease is stable over time.
    - Reproductive fitness – How often do affected individuals have children?
    - *De novo* mutation rate – How often is the p.D84H allele new in the proband?
- Studies in large databases
  - For a large population, what percentage of individuals with an allele have a phenotype of interest (infections, hematologic abnormality, frank disease).
  - This approach evens out the impact of genetic background of individual families.

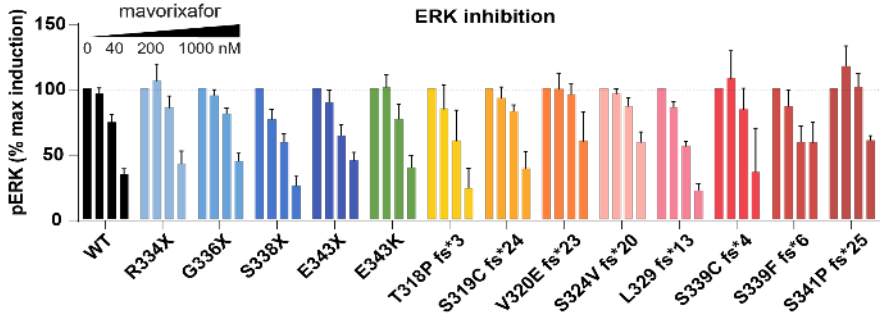
Advancing WHIM Genotype/Phenotype Research

ASH 2021: Mavorixafor inhibited Ca^{2+} mobilization and CXCL12-dependent downstream signaling in all *CXCR4* mutant cells

A

Ca^{2+} mobilization		WT	R334X	G336X	S338X	E343X	E343K	T318P fs*3	S319C fs*24	V320E fs*23	S324V fs*20	L329Q fs*13	S339C fs*4	S339F fs*6	S341P fs*25
mavorixafor	IC50 (nM)	6.3	15	11.8	7.7	8.8	19.4	7.6	39	17	37.9	19.3	8.6	26.7	18.2
	Emax (%)	84	72	82	89	90	66	88	76	65	58	51	77	59	57

B



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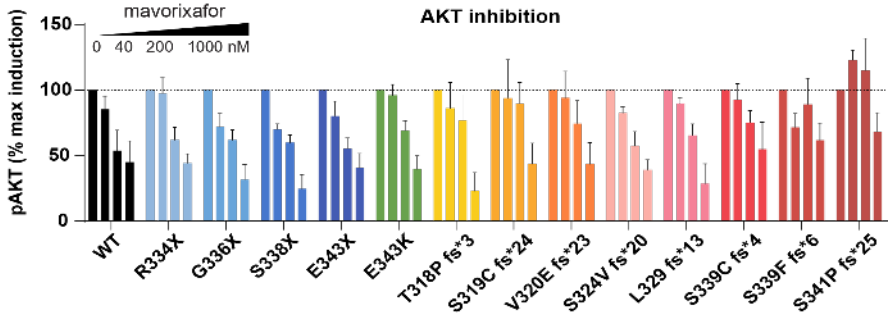


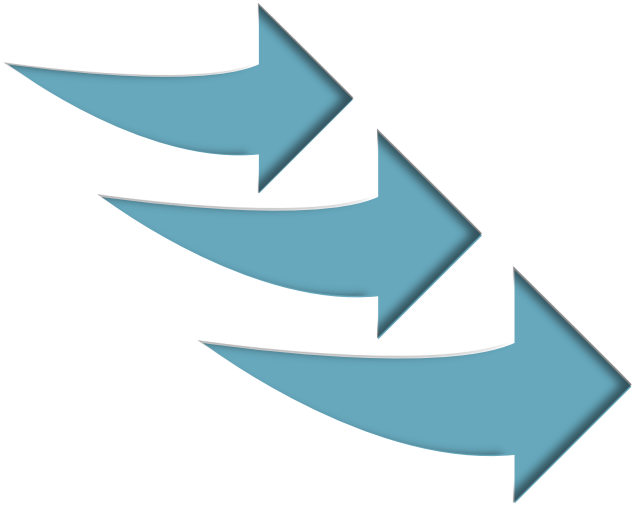
Presented at ASH 2021

- ✓ Examine **known CXCR4 mutations** and confirm "gain of function" effect at receptor level
- ✓ Confirm Mavorixafor antagonism (in vitro)
- ✓ Determine allele frequency of known mutations (level of detection >10^{-8})

Ongoing: 2022 Readout

- Examine **additional novel CXCR4 mutations and patient phenotypes** (>40 and growing)
- Confirm "gain of function" CXCR4 activity
- Confirm Mavorixafor activity
- Determine frequency of novel mutations when possible (e.g. D84H ~3.6 x 10^{-5})

Moving Forward Based on Genotype/Phenotype Success



- Understanding Penetrance
  - Focusing on D84H and others of interest
  - Family studies and working with larger databases
- Expanding Physician and Patient Education
  - Increasing Medical Science Liaisons (MSL) efforts
  - Support for international WHIM registry
  - Patient Diagnostic Liaisons (PDLs) to improve time-to-diagnosis
- Expanding Patient Support for Diagnostic Testing
  - PATH4WARD commitment
  - Testing program with existing registries (e.g. SCNIR)

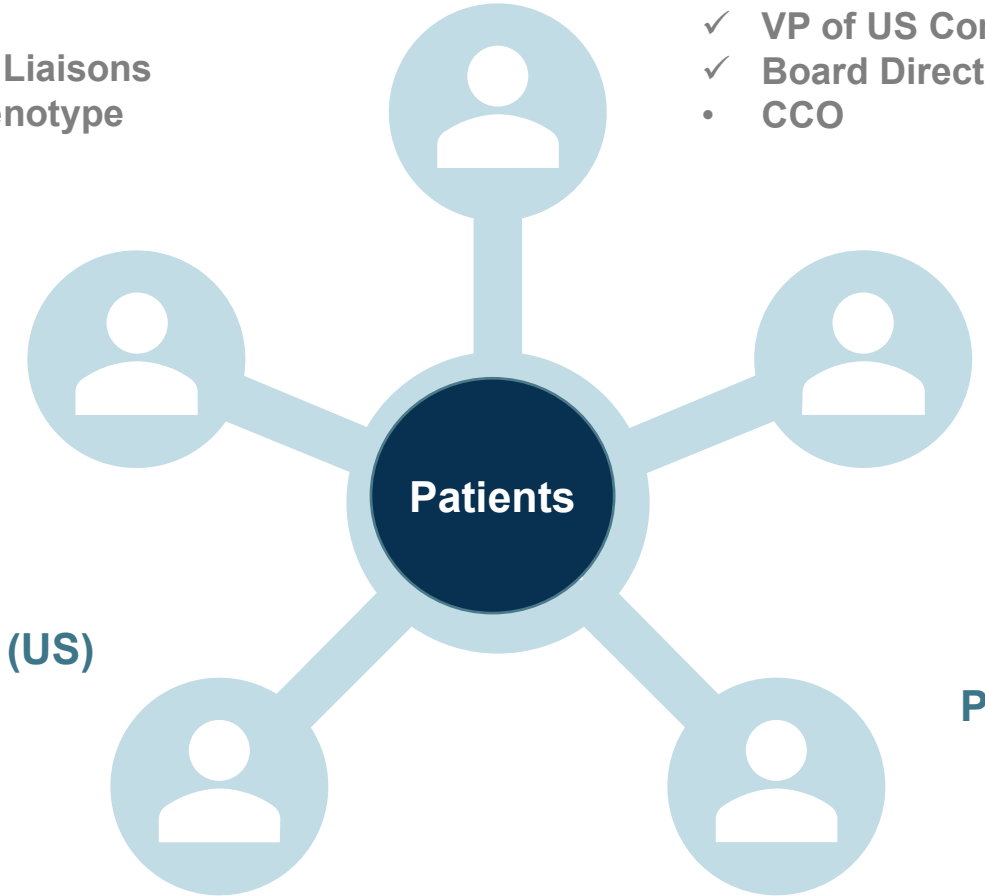
Getting Ready For US Commercial Launch; EU to Follow

Enabling Diagnosis

- ✓ Patient Diagnostic Liaisons
- ✓ VUS Genotype/Phenotype
- ✓ PATH4WARD
- • SCNIR Testing
- • EMR Research
- • Other registries

Building the Team

- ✓ MSLs and PDLs
- ✓ VP of US Commercial
- ✓ Board Director
- • CCO



Physician & Patient Education

- ✓ MSLs and PELs (2022)
- ✓ Advisory Boards
- • Digital Platforms & Outreach

Manufacturing & Distribution (US)

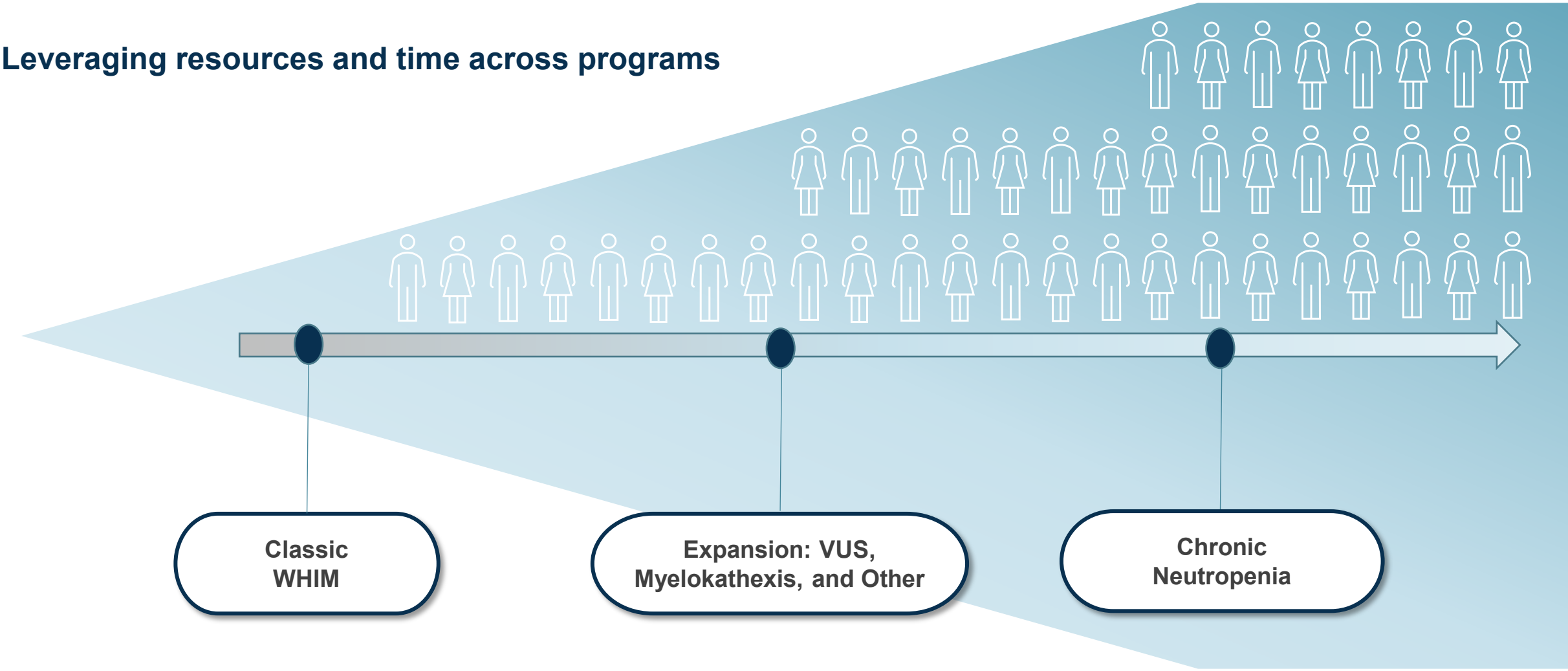
- ✓ Validation batches
- • Commercial trade dress
- • Third party logistics

Payor Engagement

- ✓ US payer research
- • EU payers
- • Market Access

Building Our Business To Support A Continuum of Mavorixafor-Treatable Patients

Leveraging resources and time across programs



Today's Agenda

Primer on Primary Immunodeficiencies - Guest Speaker: Dr. Teresa Tarrant

- A complex disease for patients and clinicians creates significant unmet needs

Mavorixafor: a new potential oral standard of care to address immunodeficiencies

- Broadly increases WBC counts to alleviate cellular deficits and infection risks regardless of mutation status

Mavorixafor and WHIM syndrome

- Fully enrolled global Phase 3 clinical trial; strong Phase 2 data de-risk regulatory pathway
- Approval in WHIM: first step toward supporting a broader package insert

New Insights on WHIM syndrome – Disease Definition and Prevalence

- A disease spectrum with broader genetic/clinical profiles / larger prevalence than previously understood
- **Guest Speaker: Dr. Neal Sondheimer**
- Expanding patient identification, physician and patient support and market access efforts

Mavorixafor and Chronic Neutropenia (CN)

- CN has high unmet need; SoC is limited and has known risks
- Promising initial Phase 1b data in CN signals expanding role for mavorixafor in additional immunodeficiencies

Fireside Chat with Dr. Tarrant – the Physician Perspective

Wrap-Up / Q&A

Chronic Neutropenia Beyond WHIM

What is Chronic Neutropenia (CN)?

Chronically immunocompromised patients due to sustained, low neutrophil counts (neutropenia)

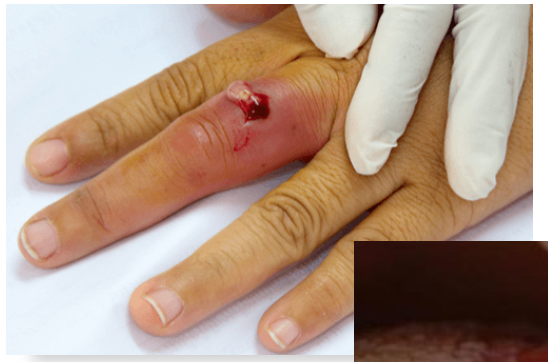
Danish Study: Prevalence and Mortality Risk[3]

- 0.06% of population with chronic neutropenia (<1,500 cells/microliter), or about 6 in 10,000
- All-cause mortality: 2.5-6.5X hazard ratio vs. non-neutropenic population

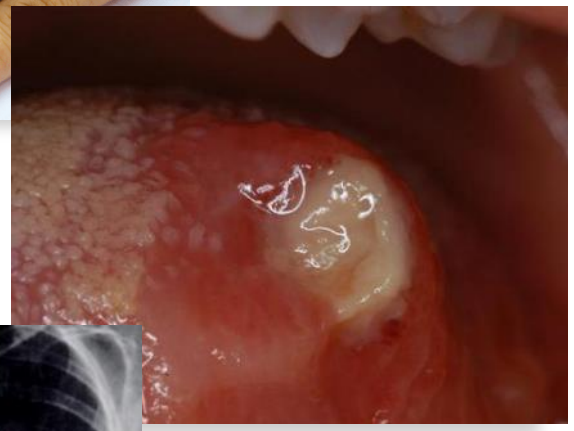
The magnitude of neutropenia correlates with higher risk of severe infections and greater frequencies of infections

- Mild if ANC between 1,000 and 1,500/µL
- Moderate if ANC between 500 and 1,000/µL
- Severe if ANC <500/µL

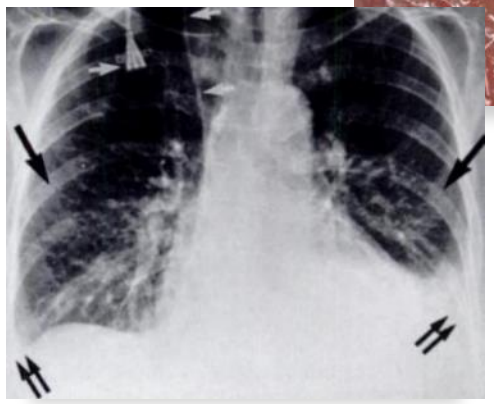
Skin Abscesses



Oral Ulcerations



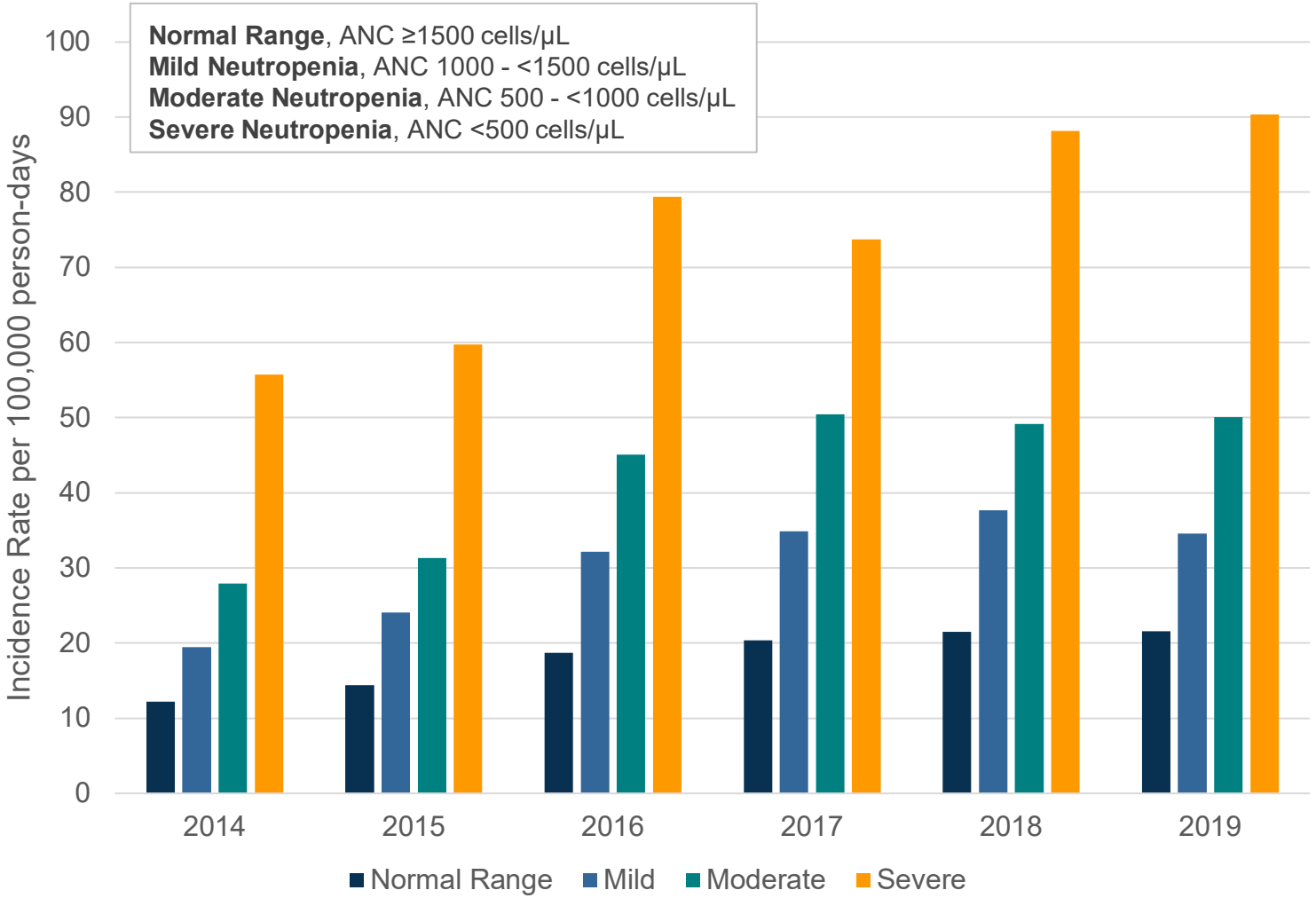
Pneumonia



1. Bodey GP et al. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med*, 1966 2. Choi *Bone Mar Trans*. vol. 35. 2005. pp. 473-477.
3. Andersen et al, *J Intern Medicine*, 2016 Jun;279(6):566-75.

U.S.-Based Research: Risk of Serious Infection Events Correlates with Neutropenia

Serious Infection Events (SIEs): Any infection that required **hospitalization, intravenous antibiotics and/or resulted in disability or death**

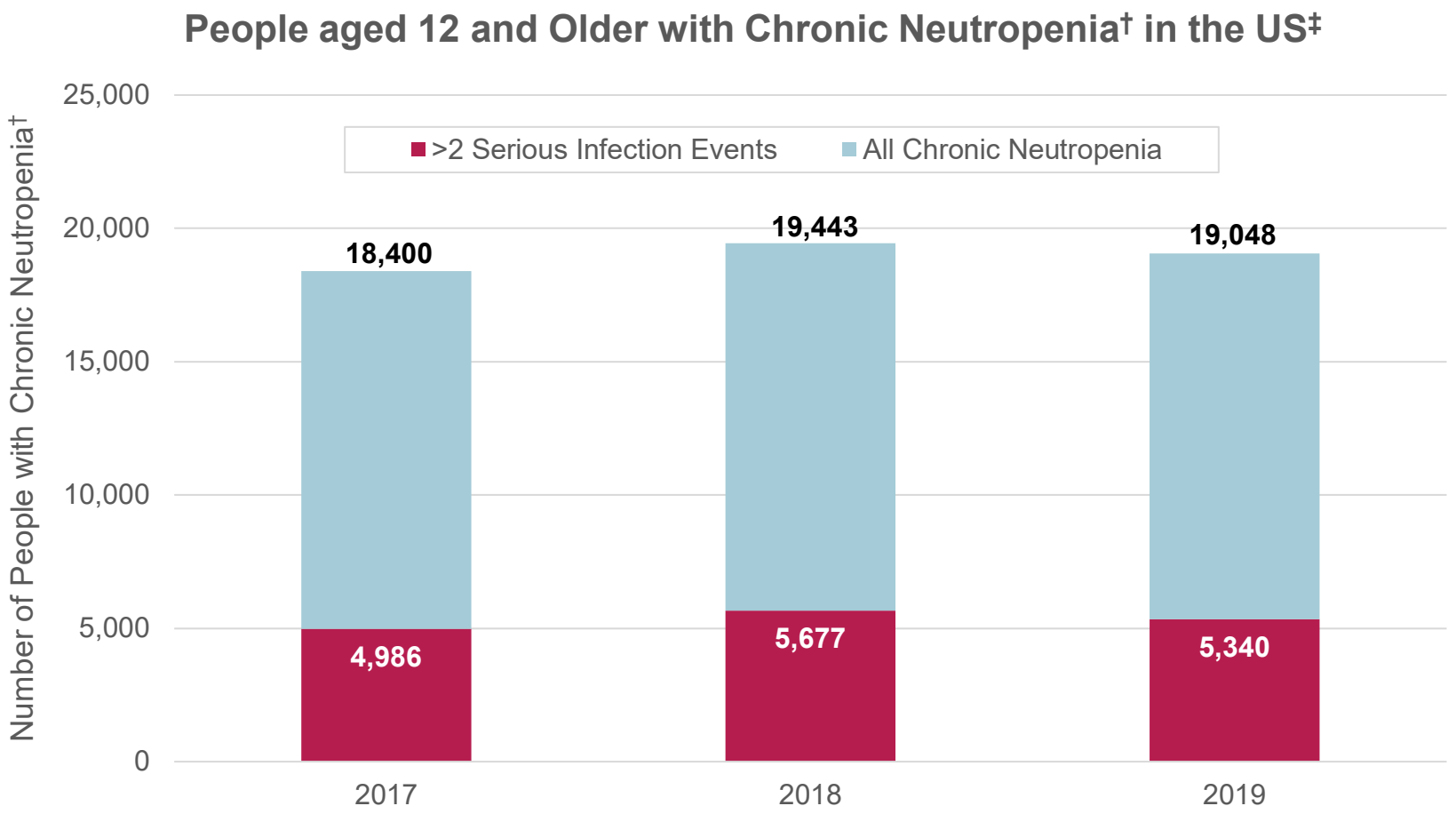


Annual incidence of SIEs for people with Chronic Neutropenia:

- At least 2-fold greater than that for general population without neutropenia
- 4-fold greater in people with severe chronic neutropenia

1. X4 Pharma EMR research, data on file.

Overall Prevalence of Patients with At Least 2 Serious Infections per Year



~25% have two or more SIEs*
(2017-2019)

Source: X4 Data on file; TriNetX USA EMR Database analysis using inclusion criteria and medical record coding, data and confirmation.

† Eligible patients in the TriNetX USA database who had an ANC <1500 cells/µl in calendar year of interest and two additional ANC <1500 cells/µl in the subsequent two years
‡ Numbers are extrapolated to reflect the total US population each year (multipliers ranged from x6.4 in 2017 to x5.2 in 2019)

Chronic Neutropenia Management: An Oral Treatment Could be Game-Changing

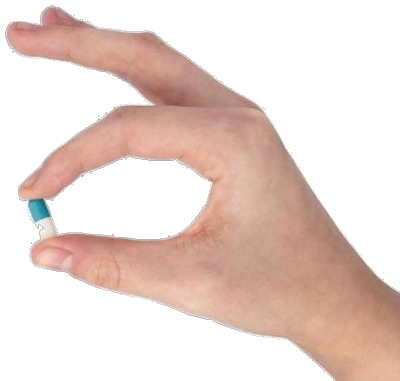
- **Injections of G-CSF:**
  - **Once or twice-daily at 5-6 μg/kg** to reduce severe neutropenia and risk of infections
  - "Dose down-titration" and reduced frequency often implemented to aid with tolerability for chronic use
  - Neutrophil target: ~1,000–2,000 cells/μL

Challenges for patients on G-CSF

- 25% continue to experience severe bacterial infections *while on chronic treatment*[1]
- Increasing risk of myelodysplastic syndromes (MDS)[2]
- ~70% have moderate or severe bone-pain impacting compliance and QoL[3]

- **No alternate therapies, except for bone marrow transplantation**
- **>2,000 patients with Chronic Neutropenia estimated to be receiving G-CSF treatment in the U.S.**[4]

Mavorixafor Potential:
an oral, once-daily Rx to reduce and/or replace G-CSF for treatment of chronic neutropenia



1.Fontbruen et al, *Blood*, October 2015 – Volume 128(14). 2. Dale et al *Support Cancer Ther* 2006 Jul 1;3(4):220-31: 3. Michniacki et al, *Blood* (2019) 134 (Supplement_1): 3449. 4. Based on X4's research of U.S. claims data, EMR and SCNIR registry data; excludes all cancer/chemotherapy-related uses of G-CSF

Ongoing Phase 1b Trial: Assessing Mavorixafor in Patients with CN

Phase 1b study: Proof of Concept in Broad CN Population

- Severe and moderate CN
- With or without genetic causes
- With or without G-CSF

Endpoints: Safety and tolerability, change in ANC (and other WBCs) vs. pre-treatment baseline

Goal: Achieve proof of concept to support FDA interactions regarding proposed registrational trial

Studying mavorixafor across broader chronic neutropenia populations

12 years or older; on or off G-CSF

Cohort A

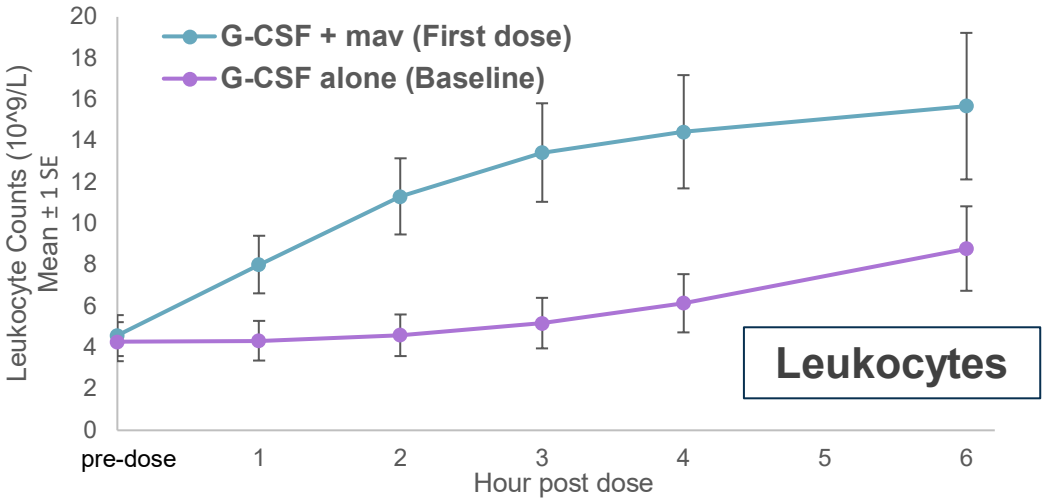
- 14 days of treatment
- Chronic idiopathic neutropenias
- Neutrophil count < 500 µL

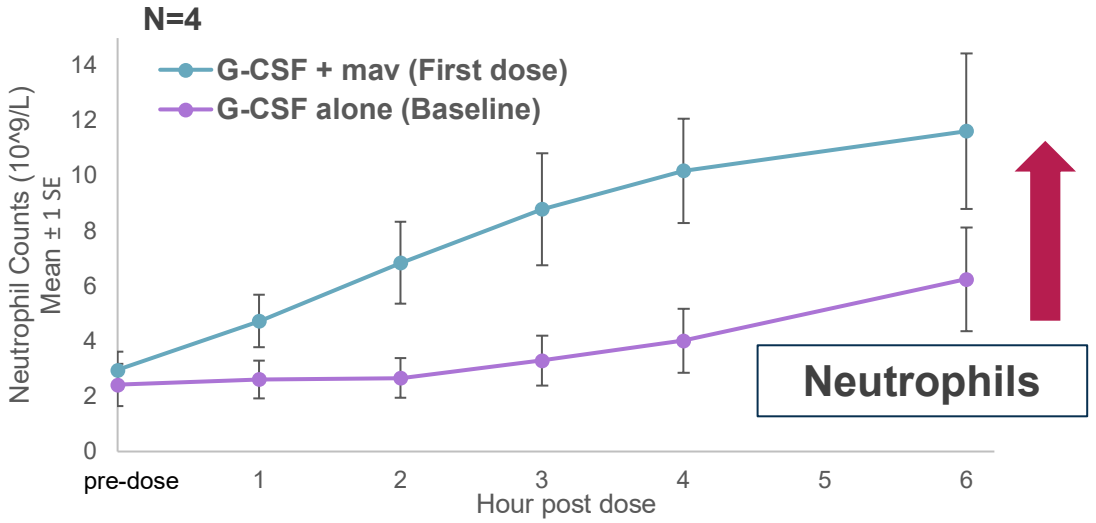
Cohort B

- 1 day of treatment
- Congenital, cyclic or idiopathic neutropenia
- Neutrophil count <1,000 µL

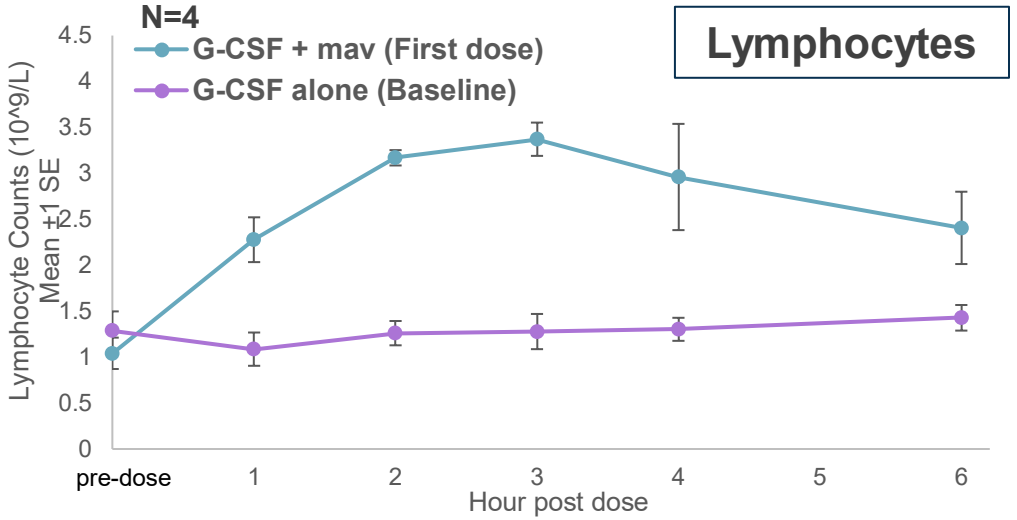
ASH 2021: Mavorixafor Impact on WBCs in Chronic Neutropenia Patients

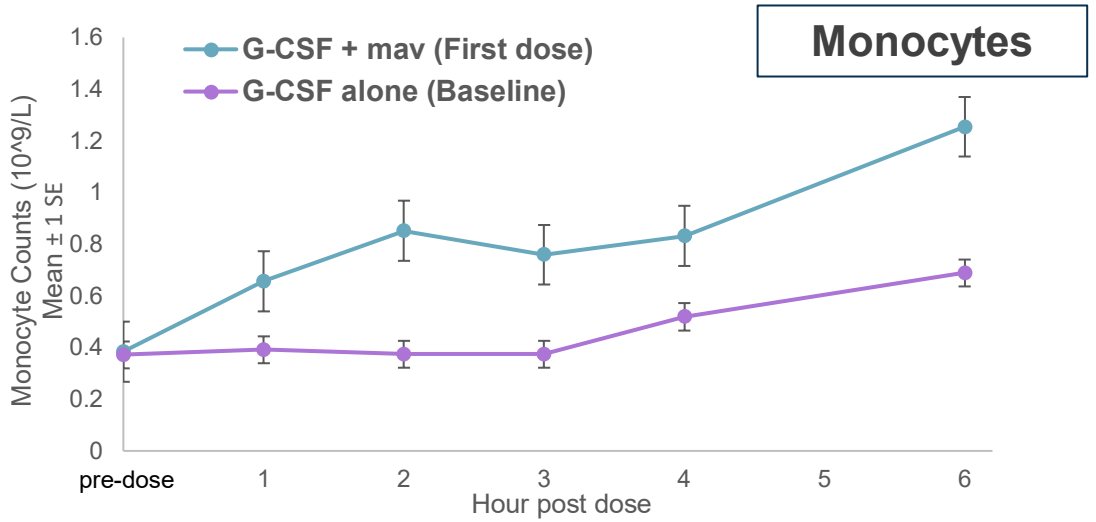
Meaningful Responses to Single Dose in Idiopathic Chronic Neutropenia Patients





Clear Increase in ANC after single dose of mavorixafor

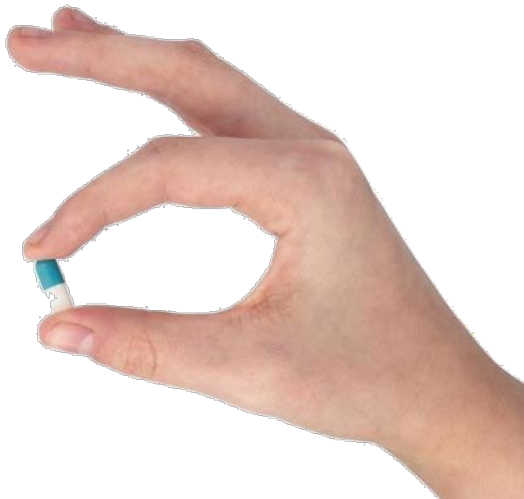




Significant Opportunity for Mavorixafor in Chronic Neutropenia (CN)

- ✓ **Many thousands of patients in the US with neutropenia** at significantly increased risk of hospitalization with severe infections
- ✓ Only available treatment is injectable, with limited tolerability and frequent injections.
- ✓ **Mavorixafor single dose proof of concept!** Initial data from the ongoing Phase 1b trial in adult patients with idiopathic CN shows clear elevation of neutrophils and all other WBCs
- ✓ Further positive data from this ongoing study could enable a pivotal study to investigate mavorixafor as the first oral treatment to reduce the risk of infections in chronic neutropenia

Ongoing Phase 1b enrolling : 2Q/3Q 2022 readout expected



Today's Agenda

Primer on Primary Immunodeficiencies - Guest Speaker: Dr. Teresa Tarrant

- A complex disease for patients and clinicians creates significant unmet needs

Mavorixafor: a new potential oral standard of care to address immunodeficiencies

- Broadly increases WBC counts to alleviate cellular deficits and infection risks regardless of mutation status

Mavorixafor and WHIM syndrome

- Fully enrolled global Phase 3 clinical trial; strong Phase 2 data de-risk regulatory pathway
- Approval in WHIM: first step toward supporting a broader package insert

New Insights on WHIM syndrome – Disease Definition and Prevalence

- A disease spectrum with broader genetic/clinical profiles / larger prevalence than previously understood
- **Guest Speaker: Dr. Neal Sondheimer**
- Expanding patient identification, physician and patient support and market access efforts

Mavorixafor and Chronic Neutropenia (CN)

- CN has high unmet need; SoC is limited and has known risks
- Promising initial Phase 1b data in CN signals expanding role for mavorixafor in additional immunodeficiencies

Fireside Chat with Dr. Tarrant – the Physician Perspective

Wrap-Up / Q&A

Teresa Tarrant, MD

- Associate Professor of Medicine, Rheumatology, and Immunology at the Duke University School of Medicine

Fireside Chat

Moderator: Dr. Diego Cadavid, X4 Chief Medical Officer

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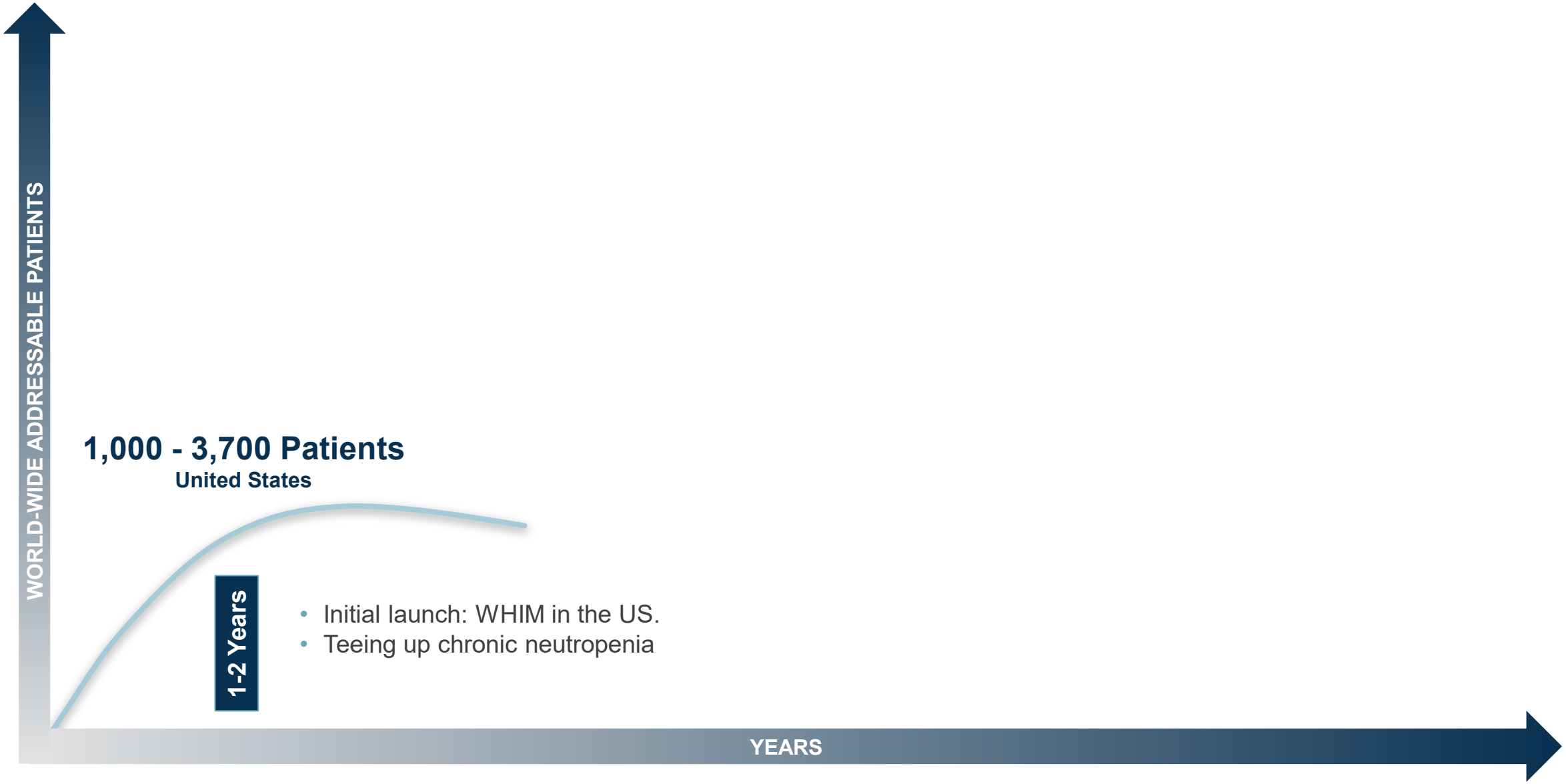
Wrap-Up / Q&A

Realizing the Potential of Mavorixafor in Immunodeficiencies

- Current treatment options for Primary Immunodeficiencies are limited
- Mavorixafor has the potential to become standard of care for certain PIs
  - Mechanism increases immune cell counts, regardless of mutation status
- Approval in WHIM would be the first step to providing a new option for patients
- WHIM syndrome has broader genetic and clinical profiles than currently recognized
  - Suggests larger prevalence than previously understood
- Mavorixafor shows promise in treating the larger population with Chronic Neutropenia
- X4 is growing to support a range of PI patients globally, near- and long-term

Primary Immunodeficiencies: Mavorixafor's First Potential Franchise



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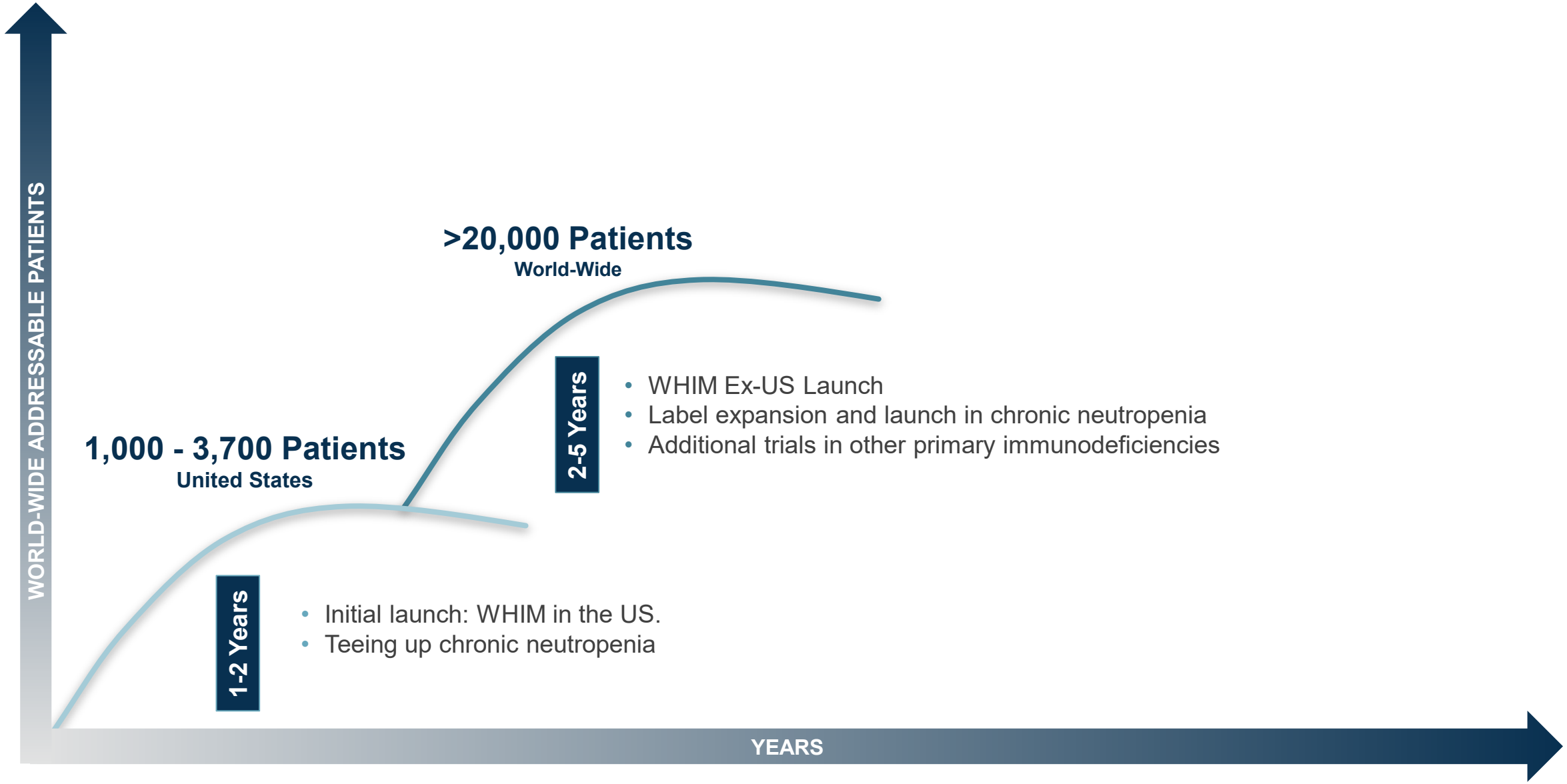

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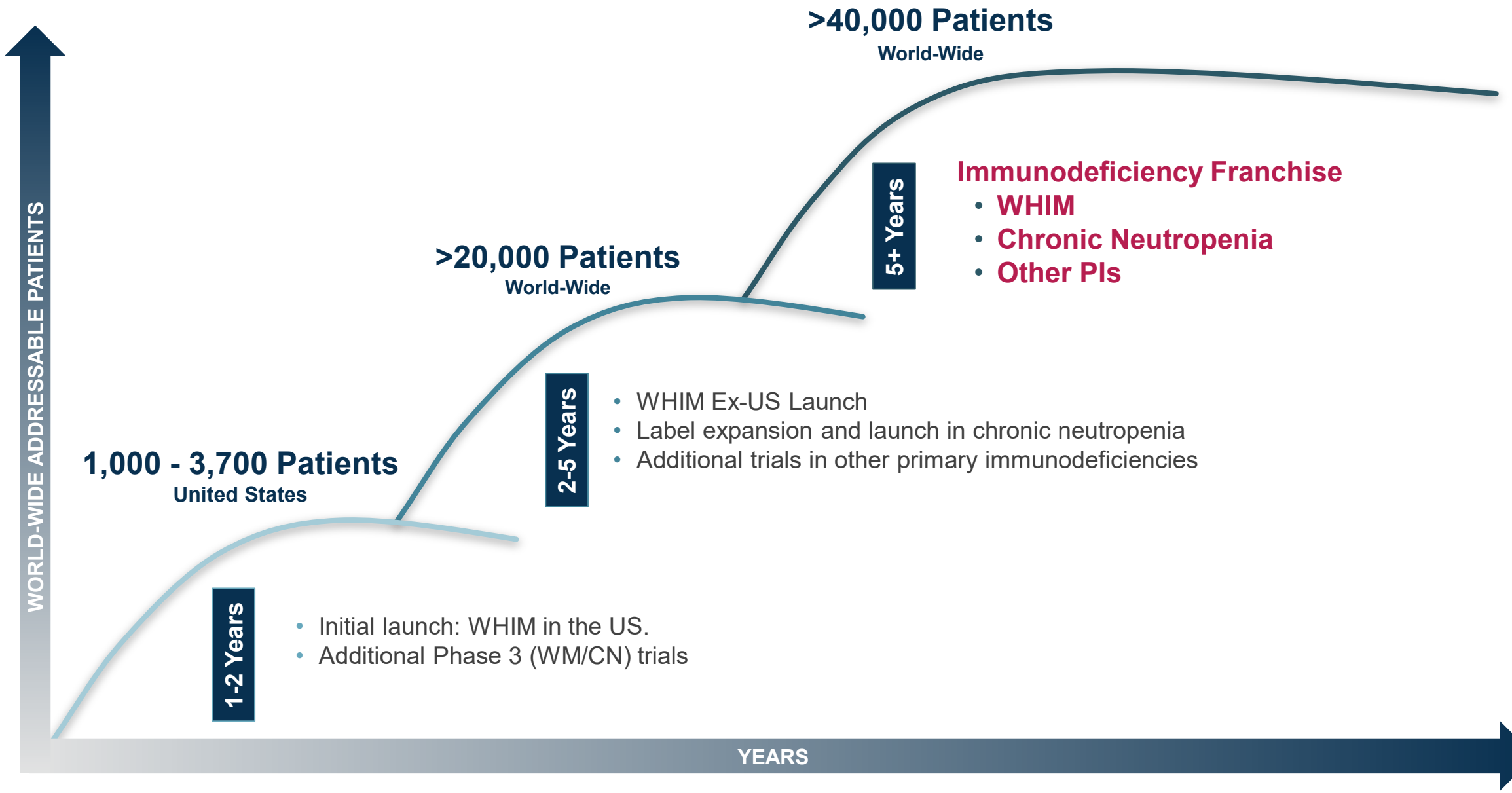


Q&A

Paula Ragan, Ph.D.
Chief Executive Officer

Diego Cadavid, M.D.
Chief Medical Officer

Art Taveras, Ph.D.
Chief Scientific Officer

Dr. Teresa Tarrant
Allergy & Immunology Specialist, Rheumatology
Duke University

Adam Mostafa
Chief Financial Officer

Dr. Neal Sondheimer
Associate Professor, Dept. of Molecular Genetics and Pediatrics, University of Toronto

Waldenström's Phase 1b Trial: Generating PoC in Patients with CXCR4^{MUT}

Inclusion: Patients with *MYD88* + *CXCR4* mutations who are naïve to ibrutinib

Design: Multi-national Phase 1b trial of mavorixafor in combination with ibrutinib (n=12 to 18)

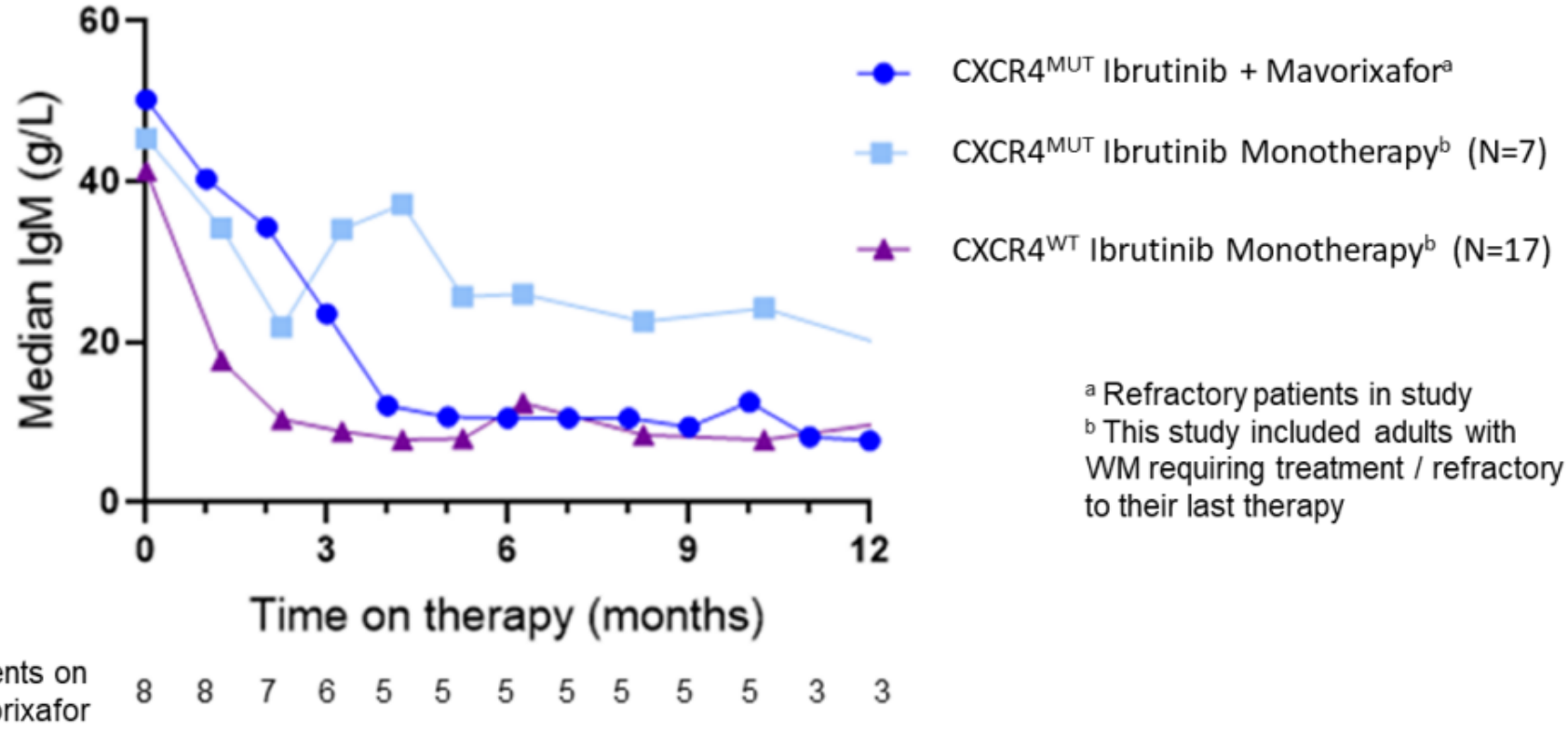
- **Intrapatient dose-escalation:** cycles of 200 mg, 400 mg, and 600 mg QD
- **3 cohorts supporting dose selection of mavorixafor:**
  - Cohorts A & B: minimum of 6 patients enrolled in each
  - Cohort C (expansion): potential for additional 6 patients dosed up to 600 mg
- **Endpoints**
  - Safety, PK/PD
  - Assessments of serum IgM levels, hemoglobin, and clinical response

LEUKEMIA & LYMPHOMA SOCIETY®

- Strategic collaboration with Leukemia & Lymphoma Society (LLS)
- Selected for LLS' Therapy Acceleration Program

ASH 2021: Data Support Mavorixafor Proof-of-Concept in Waldenström's Particularly in Refractory Patient Population

Refractory Patients' Serum IgM Levels After Treatment with Mavorixafor + Ibrutinib vs. Ibrutinib Monotherapy With or Without CXCR4 Mutations



[a] Refractory patients in study
[b] This study included adults with WM requiring treatment / refractory to their last therapy

Refractory Patients on Ibrutinib + Mavorixafor	8	8	7	6	5	5	5	5	5	5	5	3	3

Adapted from *The Lancet Oncology*, 18, Dimopoulos MA, 241-250, © 2017, with permission from Elsevier

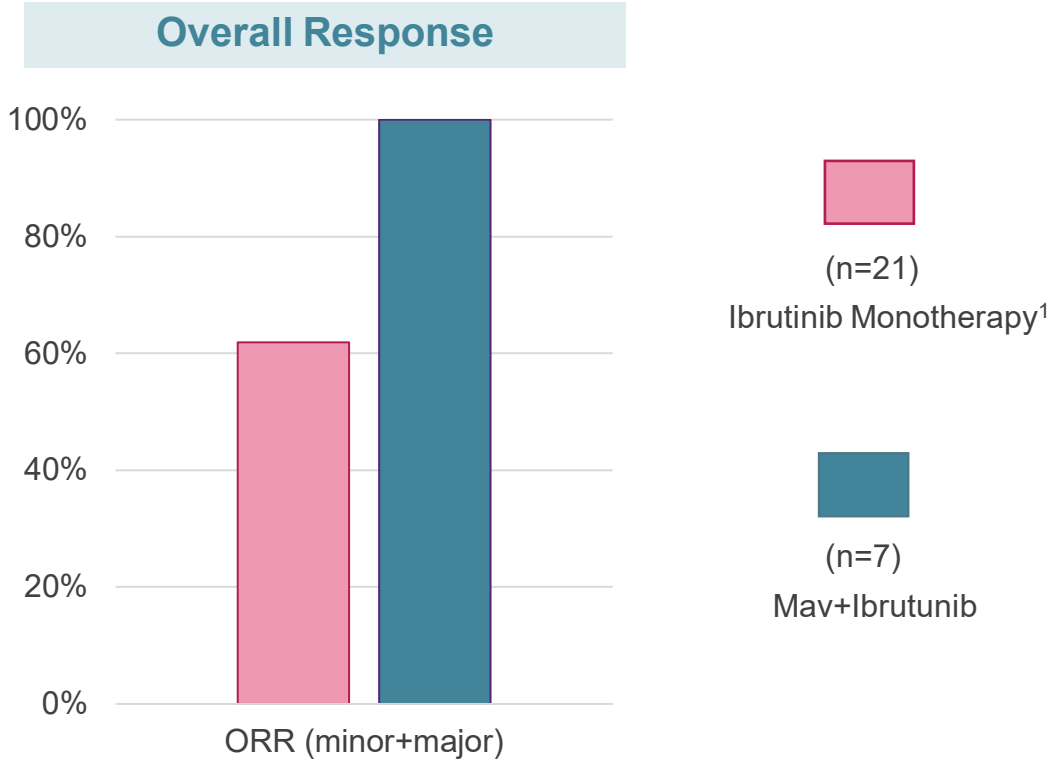
Response Rate: X4 ASH Data vs. **Benchmarks of Ibrutunib Monotherapy**
*After 6-Months of Treatment in **R/R Patients with CXCR4 Mutations***

X4 ASH 2021 Poster

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)

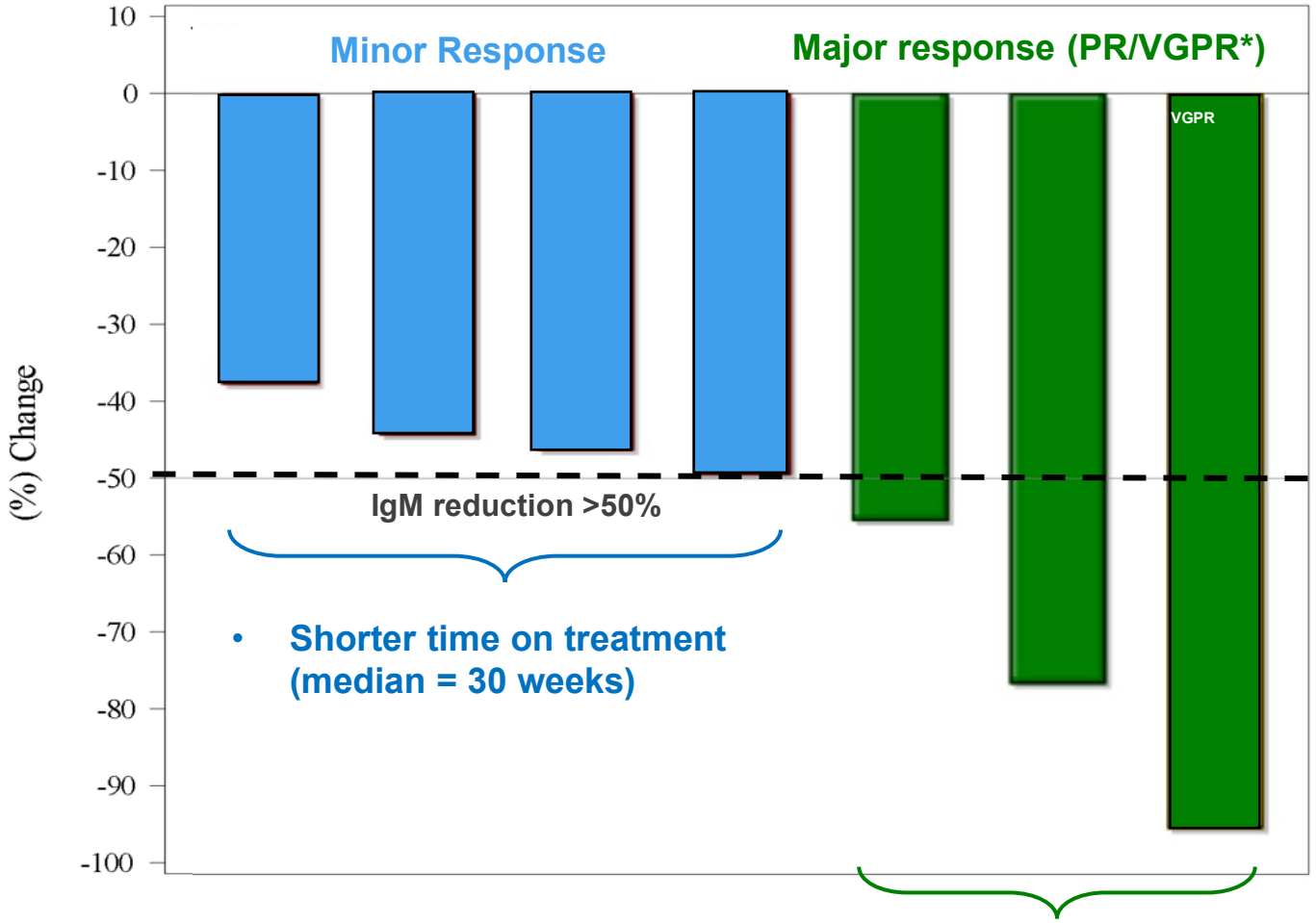
X4 ASH 2021 Vs. Benchmarks



1. Treon S et al. *NEJM*, 2015. – Figure S1(A and B) at Cycle 6 ; Note: VGPR Data are not provided; no benchmark available.

Additional Patient-Level Data from X4's Trial

Clinical Responses in Individual R/R Patients (N=7)
(based on Best IgM Response)



- Major Responses achieved after median 52 weeks on treatment
- Additional patients treated for median 30 weeks; all remain on treatment
- Highest dose (600 mg QD) is being evaluated
- Ibrutinib monotherapy benchmark = 38% major response at 6 months[1]

Major Response IgM Threshold

1. Treon S et al. *NEJM*, 2015

Patient Specific Information Related to Reported Safety in WM Phase 1b Trial

Patient with Grade 5 Fatality: 81 yo with relapsing disease

- Prior to study, **patient required plasmapheresis** and red blood cell transfusion
  - Rapidly rising IgM/cancer progression required plasmapheresis, which removes antibody and other blood components, making it harder to fight infections
- Patient entered the study with history of **recurrent respiratory infections including lung infections**
  - Resulted in prior discontinuation of rituximab
- Patient was on treatment for **less than 4 weeks** and at the lowest dose of Mavorixafor and highest dose of ibrutinib.
  - Median time of treatment for other patients was 39 weeks; most at twice the dose (400 mg QD) – no sepsis identified

Patient with Cryptococcal Infection: 71 yo

- Crypto-positive lung lesion identified before treatment
  - Demonstrating pre-existing infection
- Patient was treated for crypto and restarted study medications
- Patient **remains on-study at lower dose**

Known Safety Issues w/ Ibrutinib

- Serious infections are a risk of ibrutinib
- >50 cases of crypto reported (via FDA database)
- Aspen WMs trial: 3% (3/98) had sepsis on ibrutinib; 2/3 were fatal

No Impact to Mavorixafor Ongoing Trials

- FDA has reviewed all data including fatality; no changes recommended to any ongoing trial
- Independent Data Monitoring Committee reviewed all WM safety; no changes, dose-escalation supported
- >200 patients dosed with mavorixafor; no evidence of sepsis or cryptococcal infections
- WHIM Phase 2 study demonstrates a >60% reduction in infections while on treatment

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61 North Beacon Street
4th Floor
Boston, MA 02134

www.x4pharma.com