EHA 2021 Conference Call & Webcast

June 11, 2021

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Today's Agenda

EHA 2021 Poster EP784:

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

- **Introduction (5 min)**
  - X4 overview, focus on CXCR4, introduction to mavorixafor
- **Waldenström's Macroglobulinemia (WM) (15 min)**
  - Disease overview, unmet need
  - Phase 1b trial overview
  - EHA 2021 poster results
- **Fireside Chat with Dr. Christian Buske (20 min)**
- **Wrap-Up / Looking Ahead**
- **Q&A**

X4 Management 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

ADAM MOSTAFA
Chief Financial Officer

X4 Snapshot

X4 is leading the discovery and development of therapies to treat diseases resulting from dysfunction of the CXCR4 pathway, with a focus on rare diseases and those with limited treatment options

Mavorixafor: late-stage disease-modifying therapeutic candidate

- Phase 3 global clinical trial in WHIM syndrome ongoing (data in 2022)
- Phase 1b trial ongoing in Severe Congenital Neutropenia
- **Phase 1b trial ongoing in Waldenström's macroglobulinemia (EHA data today)**

Initial therapeutic indications target >10,000 rare disease patients

Emerging pipeline with multiple pre-clinical candidates

Leadership with deep expertise in the science of the CXCR4 pathway and in successful development and commercialization of rare disease therapeutics

Strong balance sheet with cash and equivalents expected to fund operations into the fourth quarter of 2022

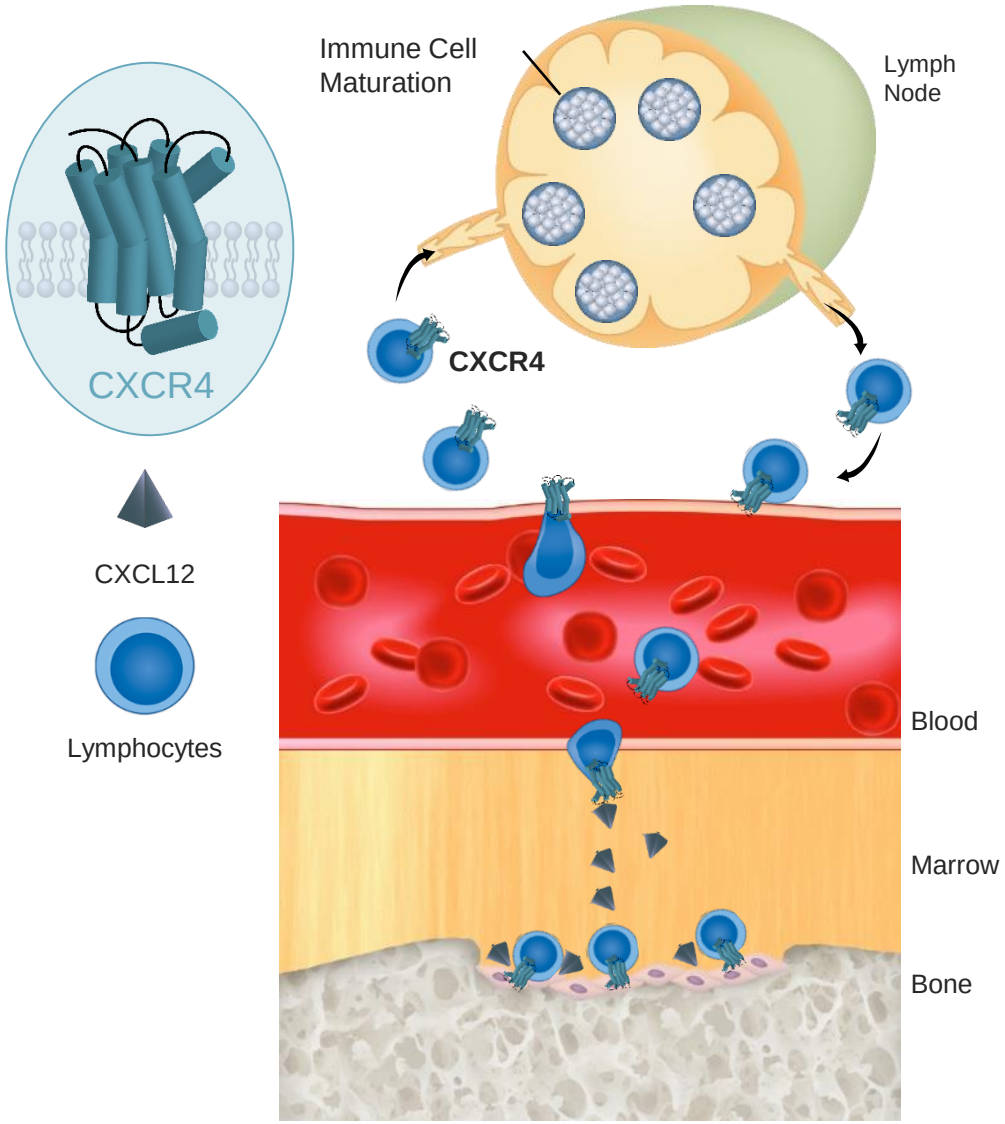
HQ in Boston with a research center of excellence in Vienna, Austria

CXCR4: a Master Regulator of Leukocyte Trafficking and Maturation

The CXCR4 receptor and its ligand CXCL12 play key roles in immune cell trafficking and immuno-surveillance

- Mutations in CXCR4 can be congenital or acquired

CXCR4 mutations in both WHIM syndrome (congenital) and Waldenström's (acquired) result in ERK hyperactivation and pronounced sequestration of immune cells in the bone marrow



Inhibition of the CXCR4 / CXCL12 pathway creates the potential for therapeutic benefit across a wide variety of diseases

- **WHIM**: mutant CXCR4 leads to pronounced neutropenia and panleukopenia
- **Waldenström's**: sequestered B-cells remain protected/ stimulated and produce elevated levels of IgM
  - CXCR4 inhibition mobilizes B-cells to periphery, enabling potential BTK inhibition and cancerous B-cell killing

About Mavorixafor: a First-in-Class CXCR4 Antagonist

First-in-class CXCR4 antagonist

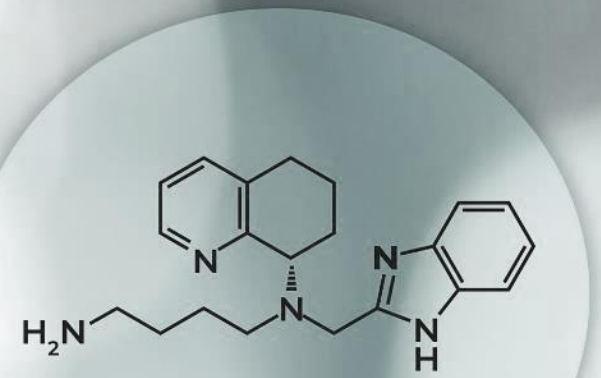
- Small molecule with high potency and selectivity
- Terminal half-life of 22 hours
- Formulated as a once-daily oral capsule

Clinical trial experience in greater than 200 patients

Regulatory Achievements

- Breakthrough Therapy Designation in U.S.
- Fast Track Designation in U.S.
- Rare Pediatric Disease Designation in U.S.
- Orphan Drug Status in U.S. and Europe

Issued U.S. composition of matter patents expected to provide protection through 2038



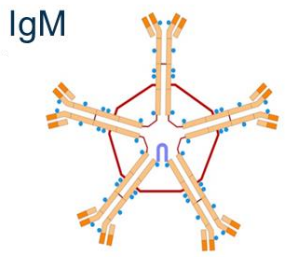
Focus on Waldenström's / EHA Poster Presentation

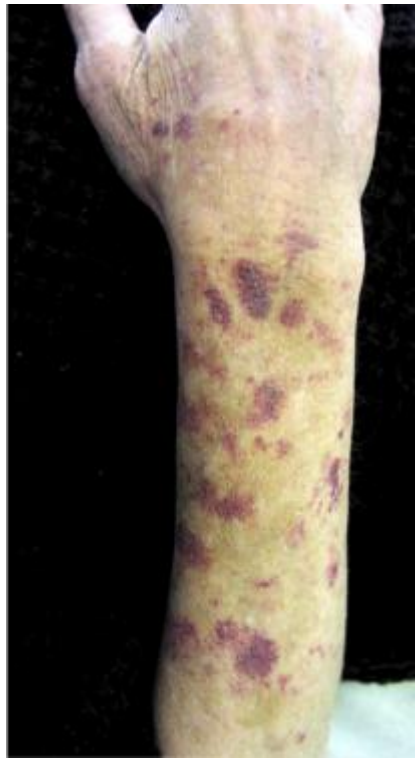
About Waldenström's Macroglobulinemia

A rare B-cell lymphoproliferative disorder of the bone marrow; a non-Hodgkin's lymphoma most often (>90%) caused by mutations in the MYD88 gene, which is involved in the body's innate immune response system

Signs and symptoms

- **Elevated IgM**
- Hyperviscosity syndrome
- Cryoglobulinemia – IgM clumping
- Pancytopenia, anemia
- Peripheral neuropathy
- Fever, night sweats, weight loss, fatigue





~8-10

year survival rate post diagnosis[1,2]

Limited Current Treatments

- Ibrutinib (BTKi)
- Chemo (bendamustine, R-CHOP)
- Rituximab
- Combinations and others

30-40%

Patients with identified WHIM-like CXCR4 mutations in addition to MYD88 mutation

Double-mutation

Waldenström's patients in the U.S. and EU[1]

~4,000-5,000

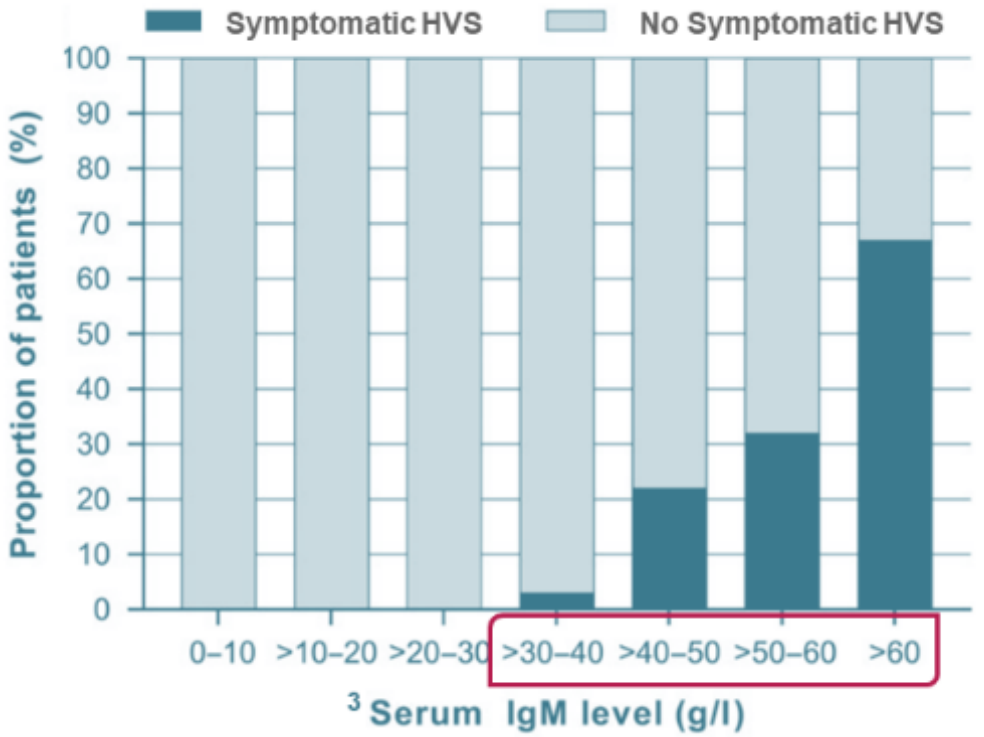
Mean progression-free survival (PFS) in CXCR4-mutation Waldenström's patients versus CXCR4-wild type[3]

<50%

1. Sekhar J, et.al., Waldenström macroglobulinemia: a Surveillance, Epidemiology, and End Results database review from 1988 to 2005. *Leuk Lymphoma* 2012;53(8):1625-1626;
2. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=33226 3. Treon *et al,* EHA 2018

Double-Mutation Waldenström's Patients Have Higher Baseline IgM and Greater Risk of Hyperviscosity Syndrome and Other Complications

Table 1[1]	CXCR4 mutation	CXCR4 wild type
Serum IgM level at diagnosis[2]	+++	+
Risk of hyperviscosity (HVS)	+++	+
Bone marrow involvement	++	+
Lymphadenopathy	+	+++
Splenomegaly	+	+
Serum beta-2-macroglobulin	+	++
Thrombocytopenia	++	+
Leukopenia	+	+
Anemia	+	+
Acquired von Willebrand disease	+++	+
Time to therapy initiation	Shorter	Longer
# of WM patients (13,000)	***4,000-5,000***	***8,000-9,000***



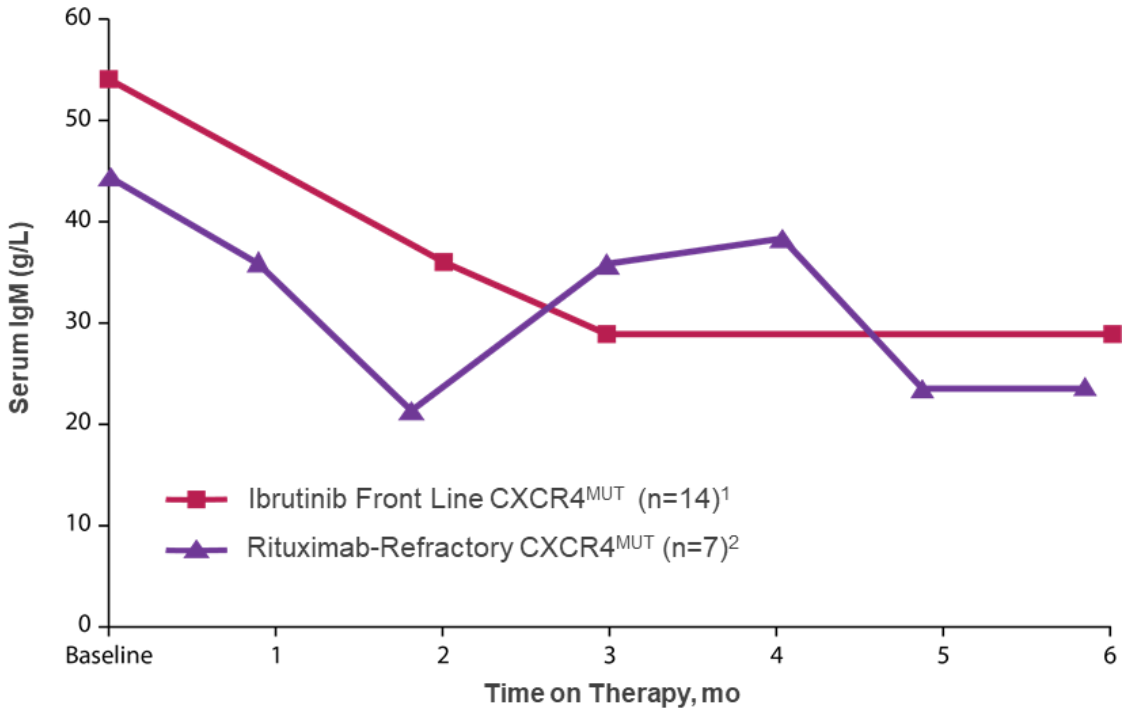
Living with HVS: Clinical Perspective

- Signs and symptoms: dizziness, vertigo, visual impairment, headache, coma, and seizures
- Retinopathy, hearing loss, cutaneous and mucosal bleeding, irreversible neurological impairment
- Plasma volume expansion

1. EXPERT REVIEW OF HEMATOLOGY 2019, VOL. 12, NO. 10, 873–881 https://doi.org/10.1080/17474086.2019.1649132
Sekhar J, et.al.. Waldenström macroglobulinemia: a Surveillance, Epidemiology, and End Results database review from 1988 to 2005. Leuk Lymphoma 2012;53(8):1625-1626; https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=33226
2. Journal Clinical Oncol 36: 2755-2761. 2018
3. British Journal of Haematology, 177, 717–725. 2017

Double-Mutation Waldenström's Patients Respond Poorly to BTK Inhibition

Ibrutinib Monotherapy Median Serum IgM Levels



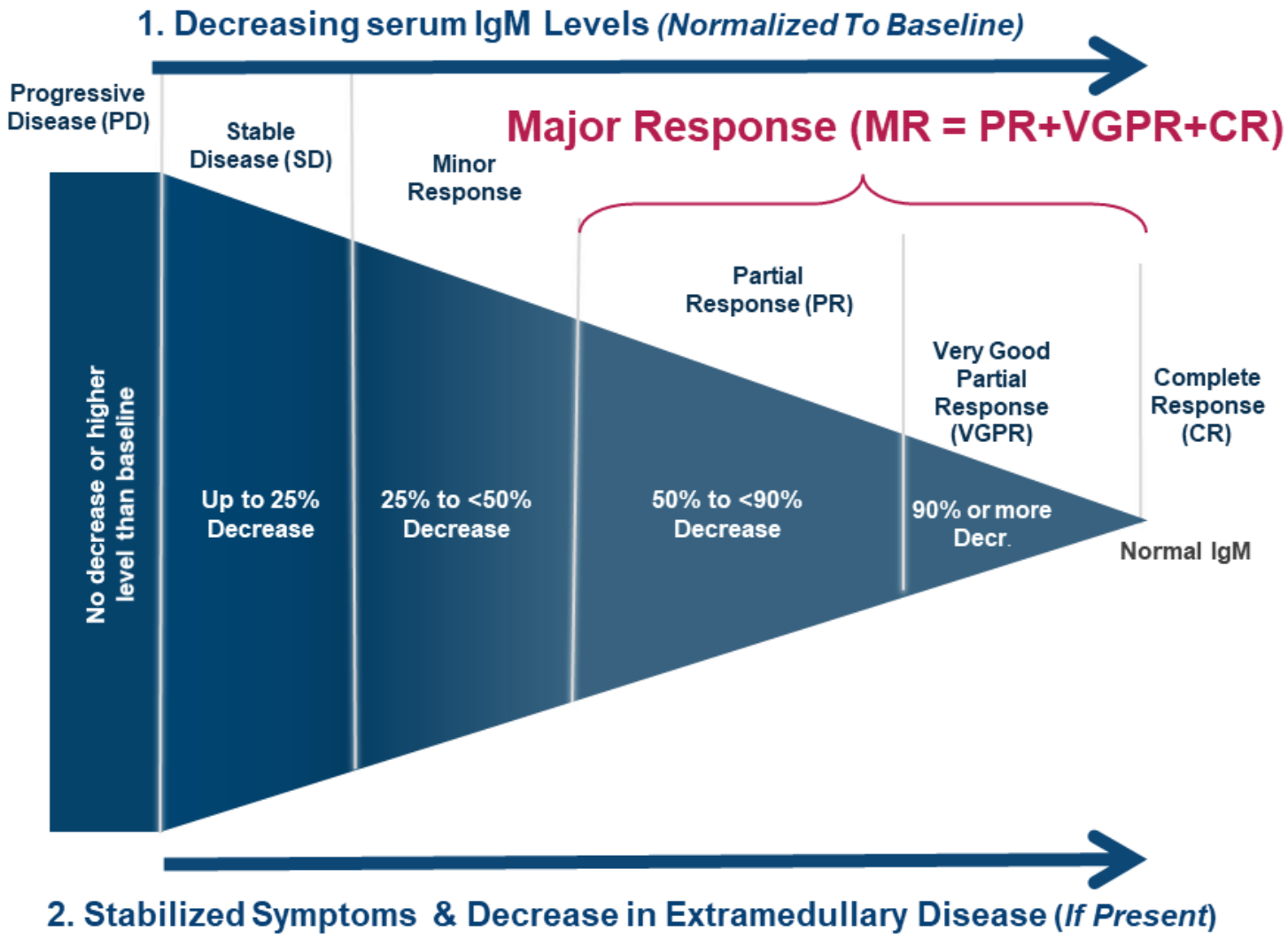
Effect of Ibrutinib Monotherapy on IgM Levels

	PREVIOUSLY TREATED[1,2]	FRONT LINE[3]
Time to >50% Response (months)	6.0	7.3
Percent at >50% reduction at 6 months	38.1%	28.6%

1, 2. Treon, NEJM, 2015, Treon, EHA, 2018; 3. Treon, JCO, 2018.

1. Treon S., et. al *JCO* 2018 DOI: https://doi.org/10.1200/JCO.2018. 78.6426
2. Dimopoulous et al, IWWM9 Meeting, 2016, *Lancet Oncology*, 2017.

Connecting IgM Reductions to Clinical Response in Waldenström's



Major Response Criteria

- **>50% reduction in normalized serum IgM**
  - using "best response"
- No new/worsening of symptoms
- Decrease (via imaging) lymphadenopathy / splenomegaly disease if present at baseline

Note: Bone marrow normalization (via BM aspirate) is required only for Complete Response evaluation

Response Assessments Require Longer-Term Study

- CT/MRI images every 3 or 6 months
- Bone marrow aspirates at 6 or 12 months or when clinically indicated

Mavorixafor Ongoing Waldenström's Phase 1b Trial

Inclusion: Adult patients with confirmed MYD88 + CXCR4 mutations who are naïve to ibrutinib

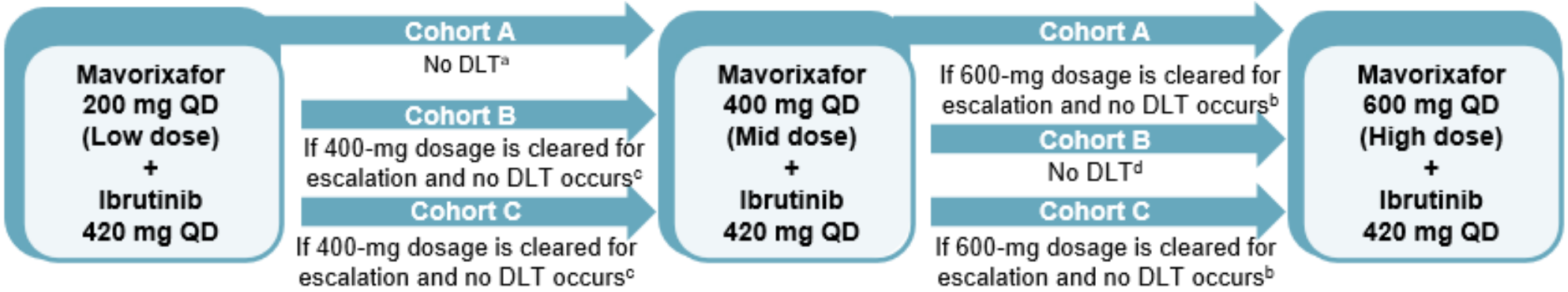
Design: Multi-national Phase 1b trial of mavorixafor in combination with ibrutinib (n=12 to 18 patients)

Endpoints:

- Safety, PK/PD, and ~monthly assessments of serum IgM levels, hemoglobin, and other blood parameters
- Objective responses assessed every 6 months

Figure 1. Trial Design (NCT04274738)

Each treatment cycle is 28 days



DLT, dose-limiting toxicity; QD, once daily.
[a]If DLT occurs, patient is withdrawn.
[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 additional patients enrolled will start at 200 mg and their doses will escalate to 600 mg.

Preliminary Phase 1b Results in EHA Poster (as of April 15, 2021)

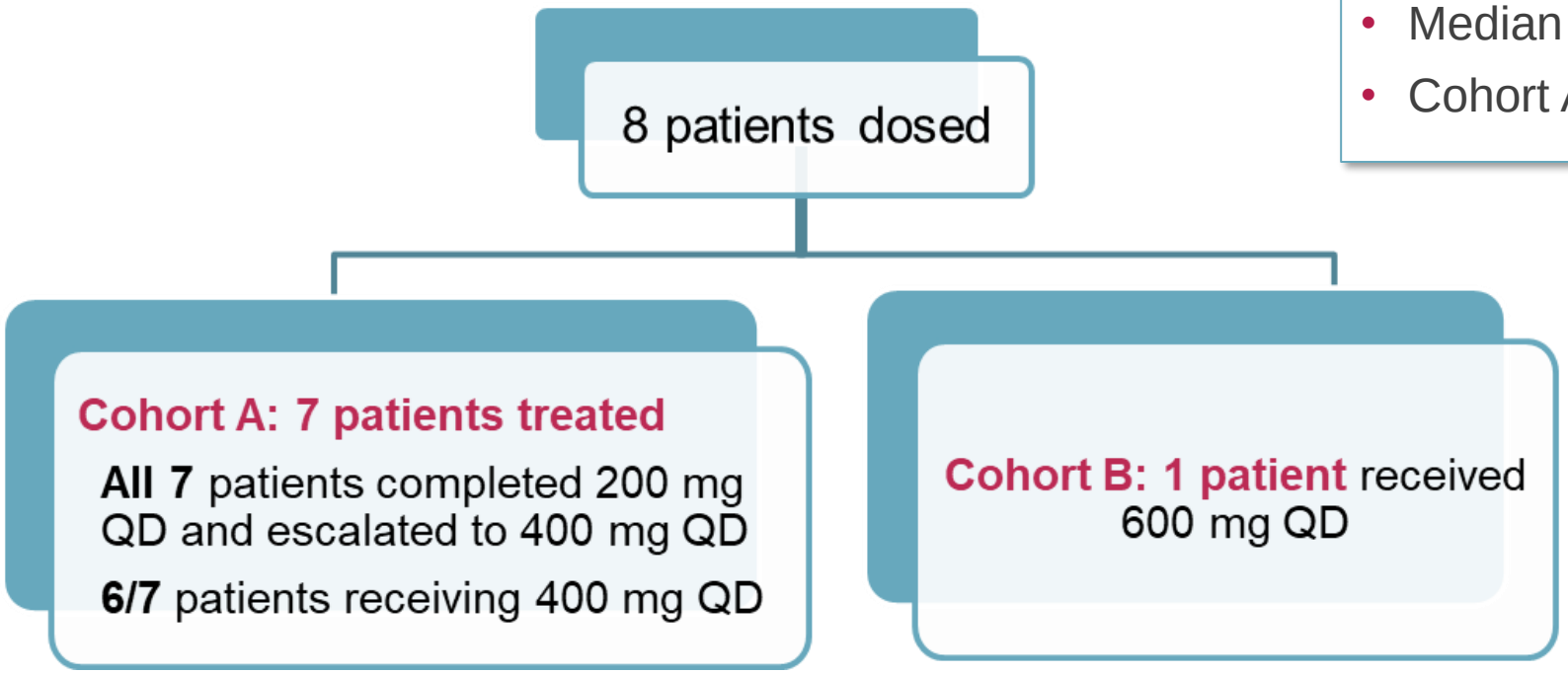
Table 1: Demographics, Clinical Characteristics and Mutational Status of All Patients

Characteristic	
Patients with both *MYD88* and *CXCR4* mutations, n (%)	8 (100)
Mean age (range), y	67 (38–80)
Male sex, n (%)	6 (75)
Mean disease duration (range), y	4.5 (0–11)
Mean prior lines of treatment, n (range)[a] Frontline therapy, n (%) Relapse/refractory therapy, n (%)	1 (0–3) 3 (37.5) 5 (62.5)
Median baseline IgM levels (range)[b], g/L	39.75 (11.88–58.50)
Median baseline hemoglobin levels (range)[c], g/L	110.5 (76–161)
Median baseline platelet levels (range)[d], 10^9/L	189 (108–453)
Patients with baseline extramedullary disease, n (%)	3 (38)
Patient baseline IPSS WM score, n	Low–2 Intermediate–3 High–3
CXCR4 mutational status Frameshift mutation, n (%) Nonsense mutation, n (%)	 4 (50) 4 (50)

IPSS, International Prognostic Scoring System
[a]3 patients were previously untreated.
[b]Normal range, 0.5–2 g/L.
[c]Normal range: male, 138–172 g/L; female, 121–151 g/L.
[d]Normal range, 150–400 10^9/L.

Preliminary Phase 1b Results (as of April 15, 2021) in EHA Poster

Figure 2. Patient Disposition



- 8 patients were enrolled in the study
- 4 patients treated for ≥6 28-day cycles
- Median duration of treatment = 156 days
- Cohort A fully enrolled, Cohort B enrolling

Mavorixafor + Ibrutinib Well Tolerated to Date

- No serious AEs were reported[a]
- 77% of AEs were mild (Grade 1)
- 18 AEs were related to combination therapy, 13 were attributed to ibrutinib treatment only and 6 to mavorixafor use only[b]
  - AEs related to use of mavorixafor only occurred in 2 patients and were grade 1 or grade 2 and included nausea, acid reflux, constipation, elevated WBC count, and worsening pain/numbness in the shoulder/hands/wrists
- 3 DLT AEs were reported in 2 patients (**Table 2**)
- Mavorixafor and ibrutinib exposures were consistent with previous single-agent studies
- No apparent drug–drug interactions between mavorixafor and ibrutinib were observed

Table 2: DLT AEs

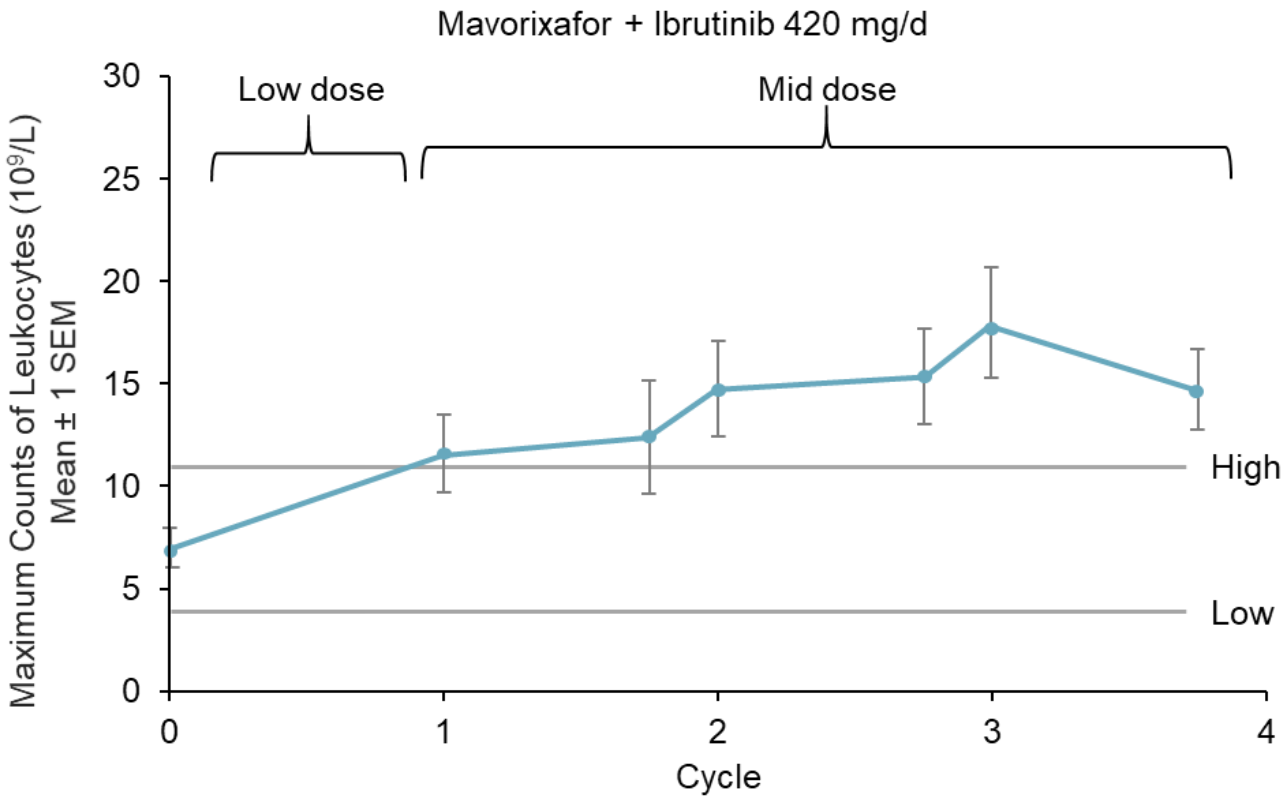
AE	Grade	Causality
Hypertension	3	Combination therapy
Worsening pain and numbness in right shoulder, bilateral hands/wrists[c]	2	Possibly mavorixafor
Worsening pain, numbness, and tingling in left hand and shoulder[d]	3	Ibrutinib

AE, adverse events; CTCAE, Common Criteria for Adverse Events; DLT, dose-limiting toxicity.
[a]Interim early data analysis performed with data cutoff at April 15, 2021.
[b]Only AEs with a completed assessment for a causal relationship to the study drug(s) at the time of the data cutoff are included.
[c]Upon review with the investigator post the data cut, the AE does not meet DLT criteria per protocol and is pending removal of the DLT flag
[d]Upon review with the investigator post data cut, the AE does not meet Grade 3 CTCAE criteria and is pending downgrade to Grade 2 and removal of the DLT flag.

Mavorixafor + Ibrutinib Induces Mobilization of Leukocytes

- Mavorixafor exposures tracked with increases in key WBC counts in all patients (**Figure 4**)
- Dose-dependent increases confirm target engagement and mavorixafor MOA
- Durable and sustained effect

Figure 4. Mobilization of Leukocytes with Mavorixafor Exposure[a]



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

Mavorixafor + Ibrutinib Effects Clinically Meaningful Decreases in Serum IgM

- All patients experienced reductions in IgM with no disease progression while on treatment

Figure 5A. Median Serum IgM Levels

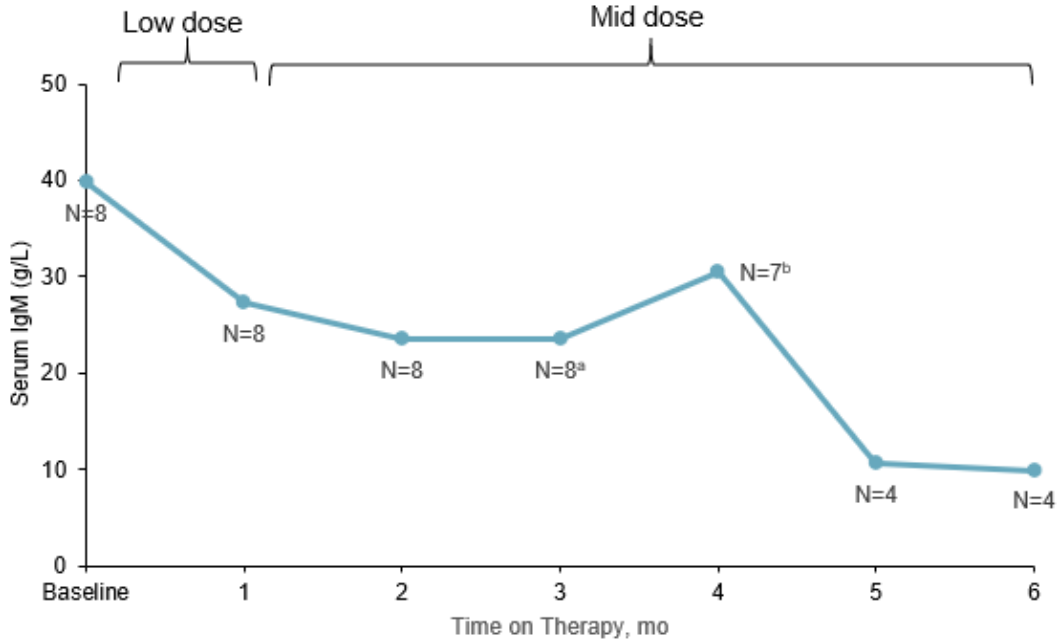
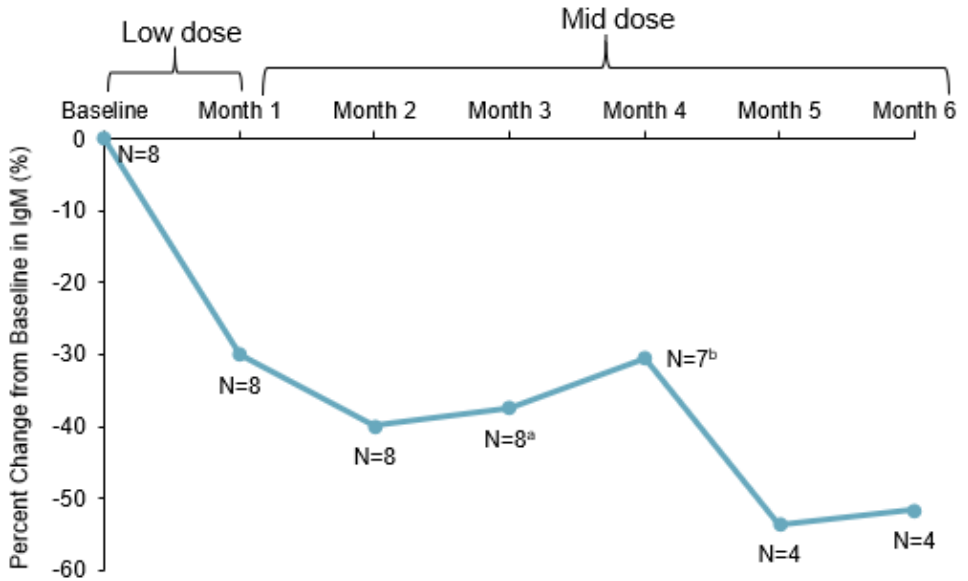


Figure 5B. Median Percentage Change From Baseline in IgM Levels



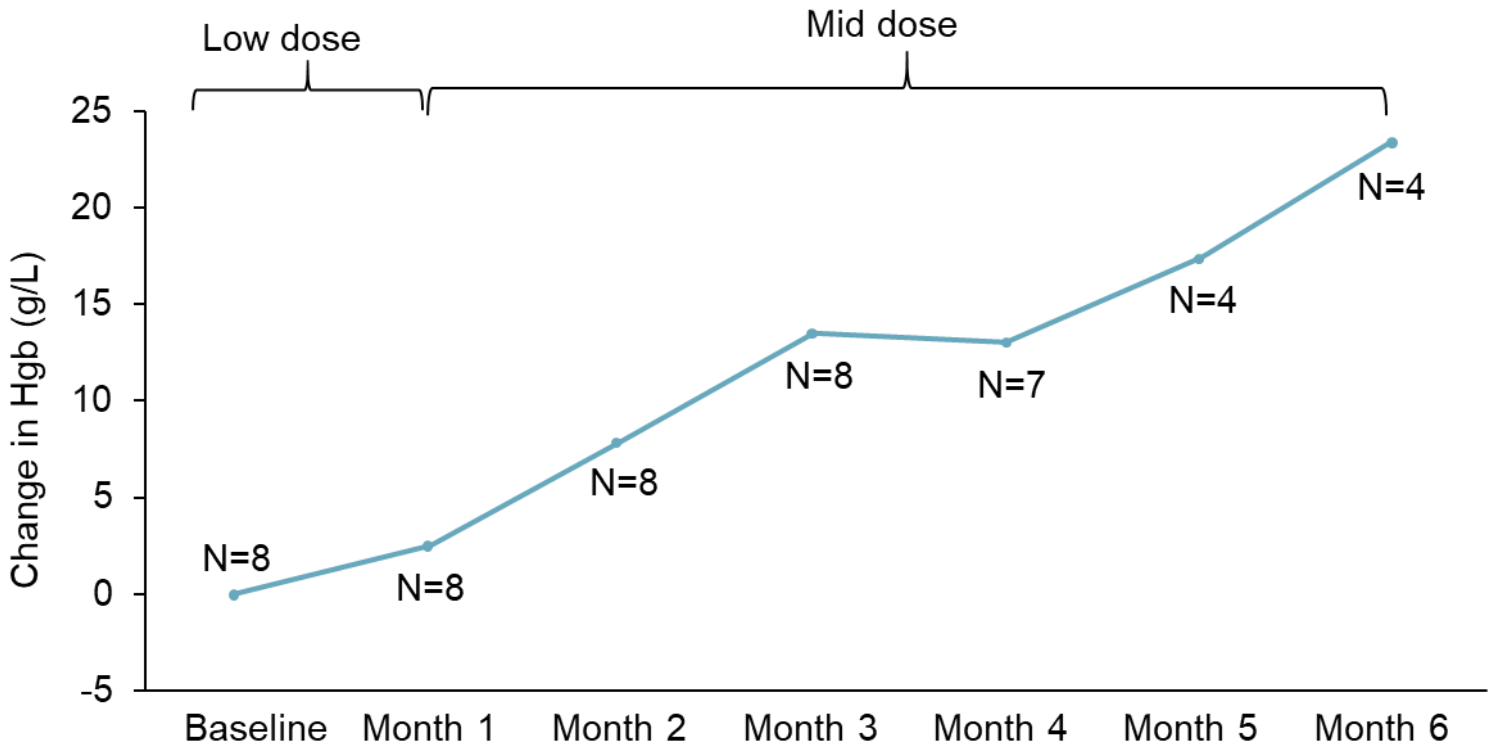
- Median absolute serum IgM levels decreased to 9.93 g/L (N=4) (range, 0.87–37.36 g/L) at 6 months from pretreatment levels

At 6 months:
- 2 of 4 patients had >50% reduction from baseline
- 1 of 4 patients had absolute IgM levels within normal range

[a] IgM data of Patient 105-001 collected on May 10, 2021, were used to ensure 3 months' follow-up time.
[b] Participant 106-001 study treatment withheld due to an AE the week prior to month 4 IgM sample collection.

Mavorixafor + Ibrutinib Increased Hemoglobin Levels Towards Normal

Figure 6. Median Change From Baseline in Hemoglobin[a]

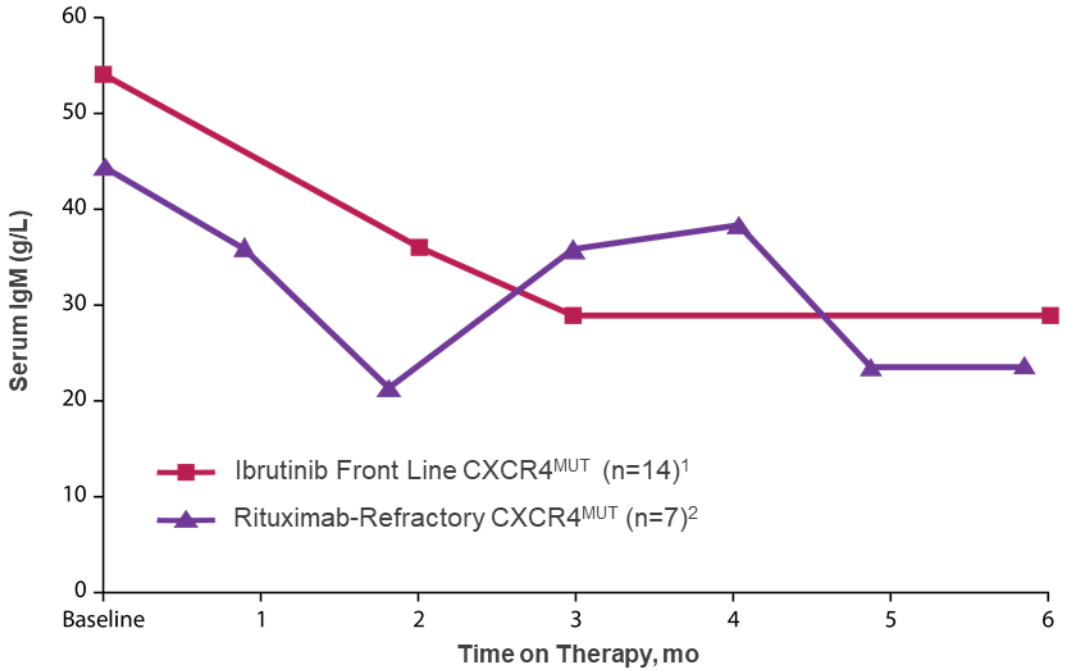


- Patients with pretreatment hemoglobin below normal had increases during treatment
- Median hemoglobin increased by >20 g/L for patients on treatment for 6 cycles (n=4) (**Figure 6**)
- Hemoglobin levels approached normal levels over time
- Key biomarker for resolution of anemia/fatigue and bone marrow health

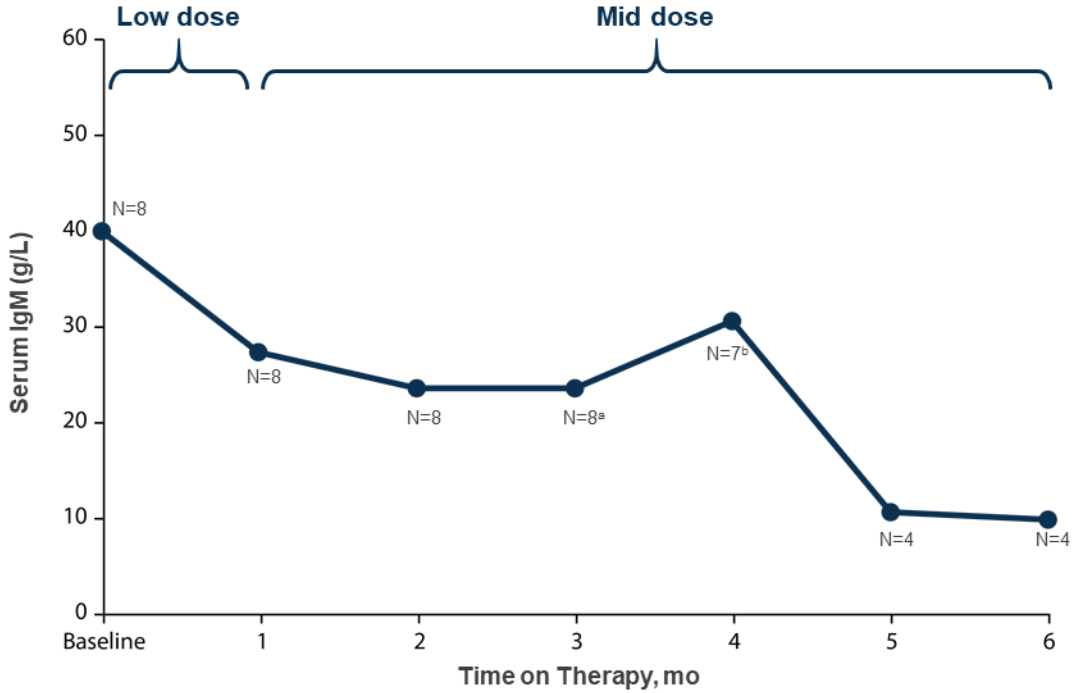
[a]Hemoglobin data of Patient 105-001 collected on May 7, 2021, were used to ensure 3 months' follow-up time.

Combo Data Suggest More Rapid and Robust Response vs. Ibrutinib Monotherapy

Ibrutinib Monotherapy Median Serum IgM Levels



Mavorixafor + Ibrutinib Median Serum IgM Levels



1. Treon S., et. al *JCO* 2018 DOI: https://doi.org/10.1200/JCO.2018. 78.6426
2. Dimopoulous et al, IWWM9 Meeting, 2016, *Lancet Oncology*, 2017.

[a] IgM data of Patient 105-001 collected on May 10, 2021, were used to ensure 3 months' follow-up time.

[b] Participant 106-001 study treatment withheld due to an AE the week prior to month 4 IgM sample collection.

Waldenström's Phase 1b Clinical Trial: EHA 2021 Poster Key Takeaways

- **Preliminary data suggest mavorixafor + ibrutinib effects clinically meaningful benefits in reduction in serum IgM and increases in hemoglobin**
- **At 6 months**, mavorixafor plus ibrutinib showed greater decreases in IgM versus previously published ibrutinib monotherapy studies at the same time point in double mutation patients:

	Ibrutinib Monotherapy	Mavorixafor + Ibrutinib
% IgM Drop from baseline	38-45%	**60-75% (4-8 patient baseline)**
≥50% Reduction	28-38%	**50% (2 of 4 patients)**

- One patient had normalized IgM by 6 months on combination treatment
  - Prior published studies of ibrutinib monotherapy in double-mutation patients show very infrequent (≤10%) reductions of this magnitude (≥ 90%) and at a median time of ~11 months on treatment
- Patient enrollment and dose escalation to the highest (600 mg QD) level continue
- Further follow-up will help define the potential and optimal dose of combination therapy to improve clinical response to BTK inhibition in double mutation Waldenström's patients

- Medical Director of the Institute of Experimental Cancer Research and Senior Consultant at the University Hospital of Ulm
- Founder and Coordinator of the European Consortium for Waldenström's Macroglobulinemia

Fireside Chat

with Dr. Diego Cadavid, X4 Chief Medical Officer and Waldenström's Expert, Dr. Christian Buske

Looking Ahead: a Catalyst-Rich Time for X4

- **Waldenström's Phase 1b clinical trial**
  - Enrollment continuing, dose escalating
  - Response measurements (CT scans and bone aspirates)
  - Additional data release(s) expected later in 2H 2021
- **Updates on WHIM Program**
  - Phase 3 enrollment update in 2Q/3Q 2021
  - Updates on WHIM prevalence and patient ID in 2H 2021
  - Longer-term data from ongoing Phase 2 open-label extension study expected late 2021/early 2022
- **Additional Program Updates Expected**
  - SCN Phase 1b trial
  - Research and Pipeline
- **2022 Expected Milestones**
  - Potential Waldenström's registrational trial
  - WHIM Phase 3 top-line data
  - Pipeline IND filing
  - Commercial ramp-up and WHIM NDA filing (4Q22/1Q23)

Q&A

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