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INCYTE - ASH 2023

Transforming the Treatment of Patients with MPNs and cGVHD

DECEMBER 11, 2023

PABLO CAGNONI

PRESIDENT & HEAD OF R&D, INCYTE

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Forward-Looking Statements

Except for the historical information set forth herein, the matters set forth in this release contain predictions, estimates and other forward-looking statements, including any discussion of the following: Incyte's potential for continued performance and growth; Incyte's potential to transform the treatment paradigm for patients with MPNs and cGVHD; expectations regarding our Opzelura franchise; expectations for next steps regarding QD ruxolitinib (XR); expectations regarding the potential and progress of programs in our pipeline, including ALK2i (INCB00928), BETi (INCB57643), mCALR MAb (INCA33989), V617Fi (INCB160058) and axatilimab; expectations regarding ongoing clinical trials and clinical trials to be initiated; expectations regarding regulatory filings and approvals, including the planned submission of a BLA for axatilimab by year-end 2023 (and the anticipation of regulatory approval in 2024); and our expectations regarding future news flow items.

These forward-looking statements are based on Incyte's current expectations and subject to risks and uncertainties that may cause actual results to differ materially, including unanticipated developments in and risks related to: further research and development and the results of clinical trials possibly being unsuccessful or insufficient to meet applicable regulatory standards or warrant continued development; the ability to enroll sufficient numbers of subjects in clinical trials and the ability to enroll subjects in accordance with planned schedules; determinations made by the FDA and other regulatory agencies; Incyte's dependence on its relationships with and changes in the plans of its collaboration partners; the efficacy or safety of Incyte's products and the products of Incyte's collaboration partners; the acceptance of Incyte's products and the products of Incyte's collaboration partners in the marketplace; market competition; unexpected variations in the demand for Incyte's products and the products of Incyte's collaboration partners; the effects of announced or unexpected price regulation or limitations on reimbursement or coverage for Incyte's products and the products of Incyte's collaboration partners; sales, marketing, manufacturing and distribution requirements, including Incyte's and its collaboration partners' ability to successfully commercialize and build commercial infrastructure for newly approved products and any additional products that become approved; greater than expected expenses, including expenses relating to litigation or strategic activities; variations in foreign currency exchange rates; and other risks detailed in Incyte's reports filed with the Securities and Exchange Commission, including its annual report for the year ended December 31, 2022, and subsequent quarterly filings. Incyte disclaims any intent or obligation to update these forward-looking statements.

Incyte at ASH 2023 Agenda

12:00-1:00 pm	Pablo Cagnoni, MD	**Welcome and Introduction**
	Ross Levine, MD	**Myeloproliferative Neoplasms (MPNs): Treatment and Novel Therapeutics in Development**
	John Mascarenhas, MD	**Zilurgisertib (ALK2i), BETi (INCB57643)** Combination opportunities with ruxolitinib
	Patrick Mayes, PhD	**mCALR MAb (INCA33989)** Development of an anti mutant-CALR mAb as potential treatment for MF and ET
		JAK2V617Fi (INCB160058) Development of a JAK2V617F inhibitor as potential treatment for MF, ET and PV
	Peter Langmuir, MD	**Axatilimab[1] (anti-CSF-1R)** Safety and efficacy of axatilimab at 3 different doses in patients with chronic graft-versus-host disease (AGAVE-201)
1:00-1:30 pm	**Q&A**	

1. Clinical development of axatilimab in GVHD conducted in collaboration with Syndax Pharmaceuticals.

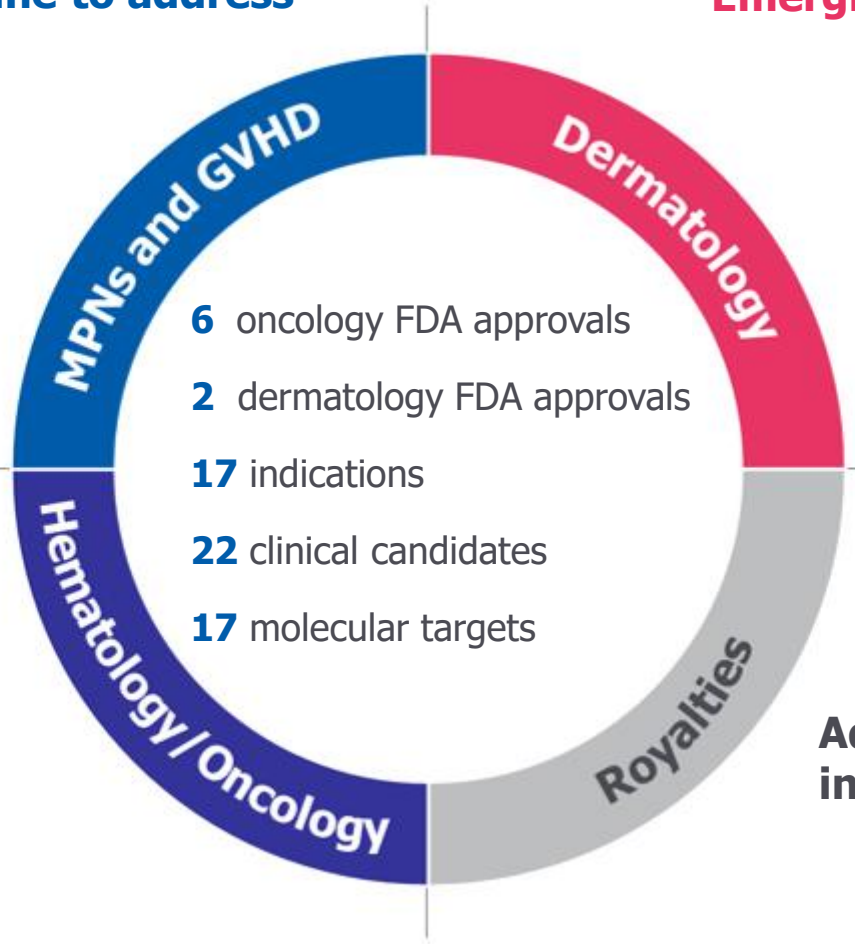
R&D Productivity Across Four Segments Driving Long-Term Growth

Leader with Jakafi and robust pipeline to address broader patient population

- *Axatilimab*
- *BETi*
- *Zilurgisertib (ALK2i)*
- *mCALR MAb*
- *JAK2V617Fi*
- *Ruxolitinib XR (QD)*

High potential oncology pipeline

- *Oral PD-L1i*
- *CDK2i*
- *LAG-3 x PD-1 BsAb*
- *TFGβR2 x PD-1 BsAb*



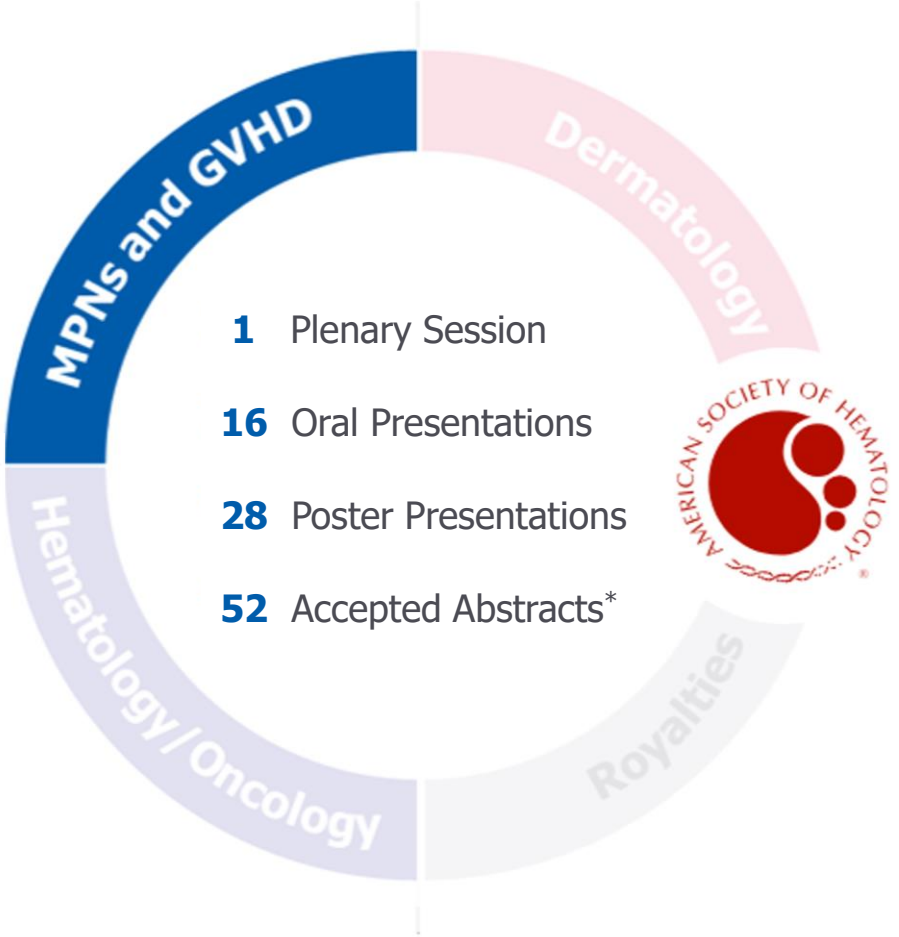
Emerging franchise led by Opzelura

- *Ruxolitinib Cream*
- *Povorcitinib*
- *IL-15Rβ MAb*

Additional growth from new indications and geographies

Mab= monoclonal antibody; BsAb= bispecific antibody

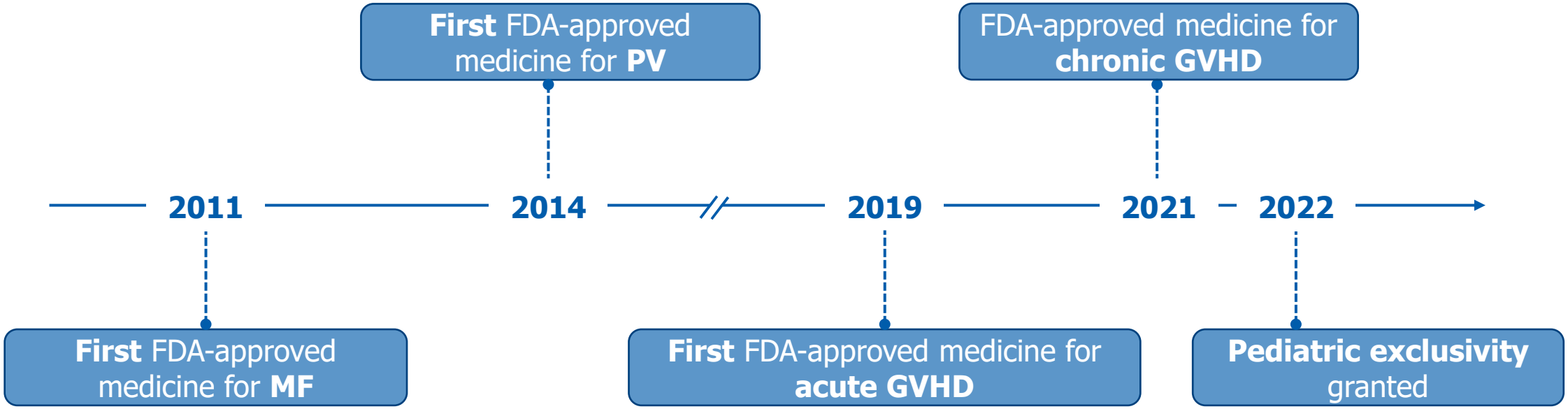
Incyte Representation and Key Presentations at ASH 2023



Plenary Session	**Axatilimab** for cGVHD (AGAVE-201)
Oral Presentations	**BETi** ± **ruxolitinib** in myelofibrosis **Zilurgisertib (ALK2i)** ± **ruxolitinib** in myelofibrosis **Ruxolitinib** for cGVHD (REACH3) **JAK2V617Fi** in MPNs

* 6 abstracts are publication only. Figures above included Incyte, alliance and study investigator sponsored.

Jakafi Has Redefined the Treatment Landscape in MF, PV and GVHD



MF= myelofibrosis; PV= polycythemia vera; gvhd= graft-versus-host disease

Transforming the Treatment of Patients with MF, PV and ET

Foundation of Therapy for MF and PV

Jakafi® ruxolitinib (tablets)

>16,000 patients on therapy[1]

2023 Net Sales Guidance **$2.59 - $2.62 billion**

Building on Jakafi through Combinations in MF

Jakafi® ruxolitinib (tablets) | **Rux XR**

\+

ALK2i **BETi**

Potential for:

- Improved spleen and symptom response
- Hemoglobin improvement and optimal ruxolitinib dosing

>8,000 additional patients could benefit

Current Development Approach

Disease-Modifying Potential for MF, PV and ET

mCALR **V617F**

Potential for:

- Allele burden reduction
- Mutant clone elimination
- Disease modification
- Functional cure

- New indication in ET

>200,000 patients with MF, PV and ET

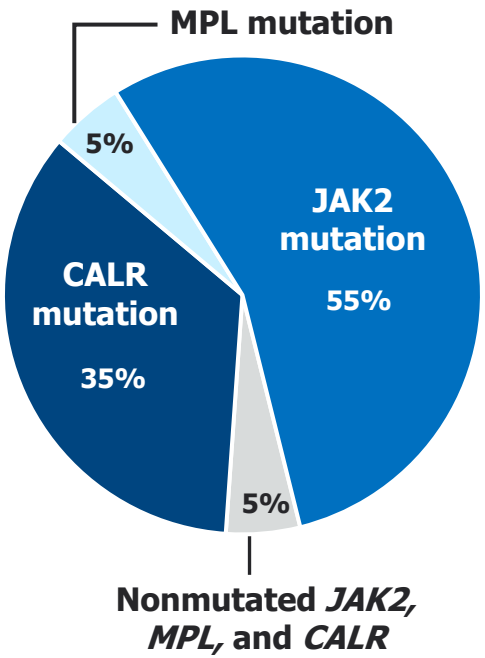
Transformational Approach

MF= myelofibrosis; PV= polycythemia vera; ET= essential thrombocythemia

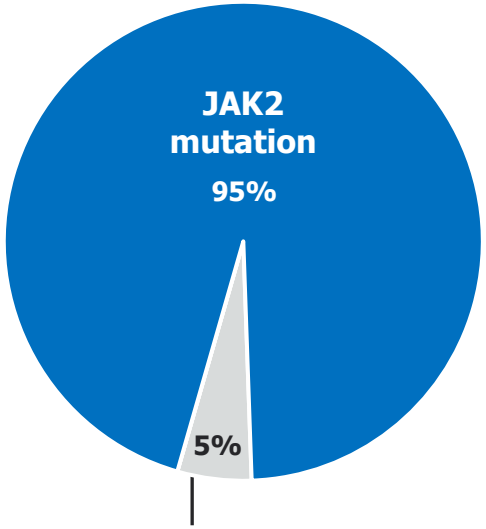
1. Includes MF, PV, and other patients; excludes GVHD (as of September 30, 2023)

Majority of Patients with MPNs can Benefit by Targeting CALR and JAK2 Mutations

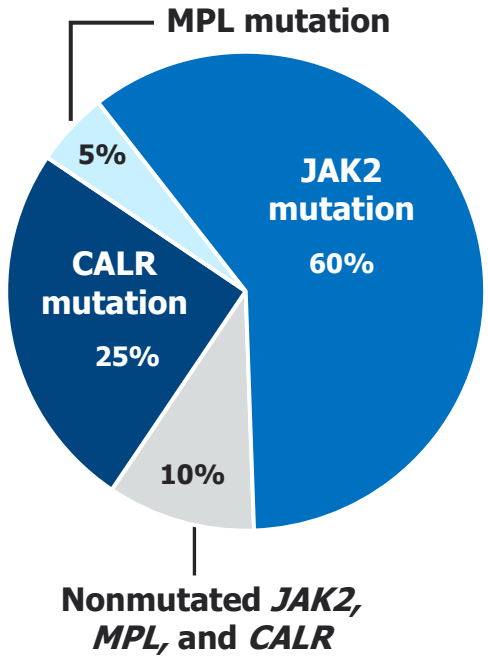
Primary Myelofibrosis



Polycythemia vera



Essential Thrombocythemia



Patients in the U.S.	~25,000 patients	>100,000 patients	>100,000 patients

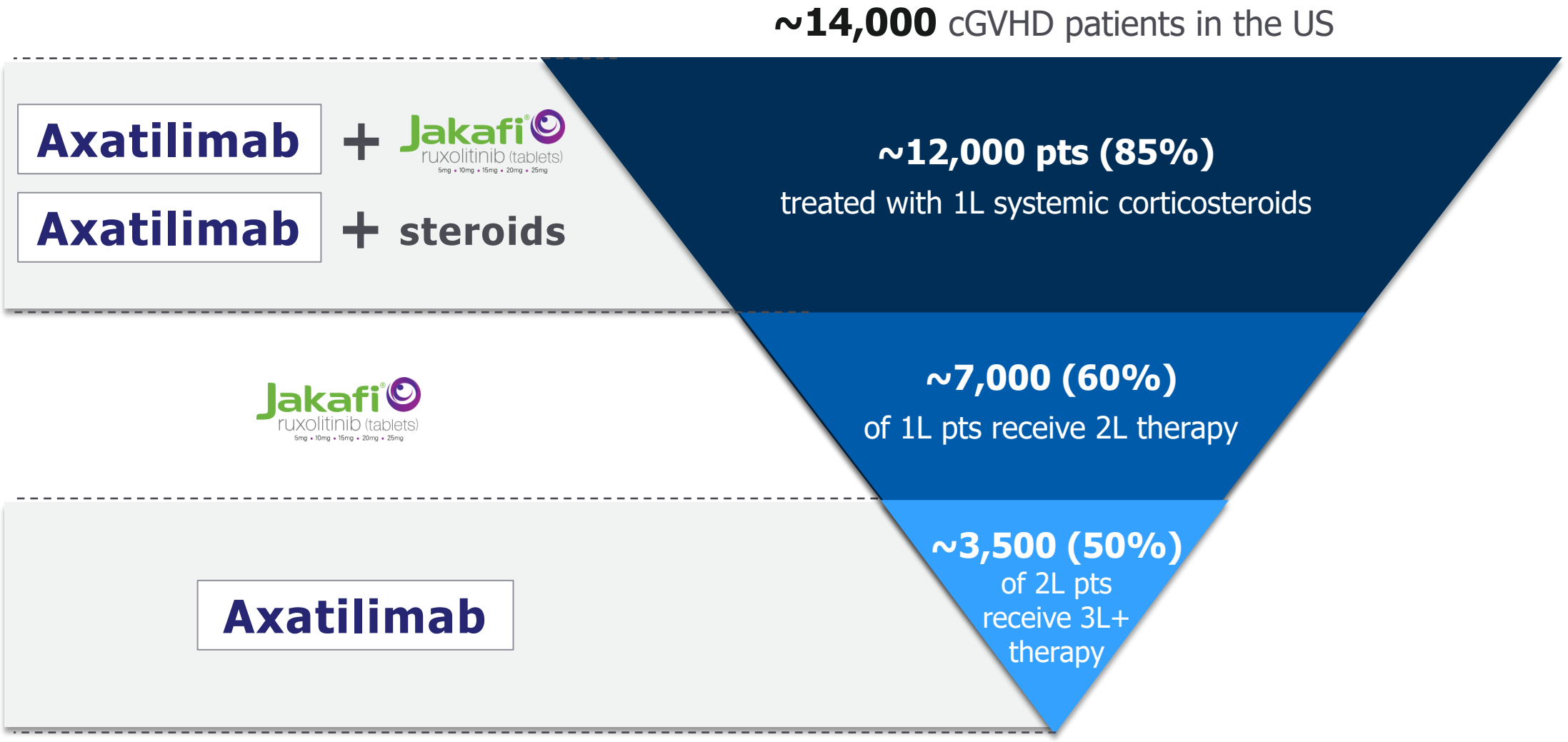
Incyte

Adapted from Klampfl T, et al. N Engl J Med. 2013;369:2379-2390.

QD Ruxolitinib (XR) Next Steps

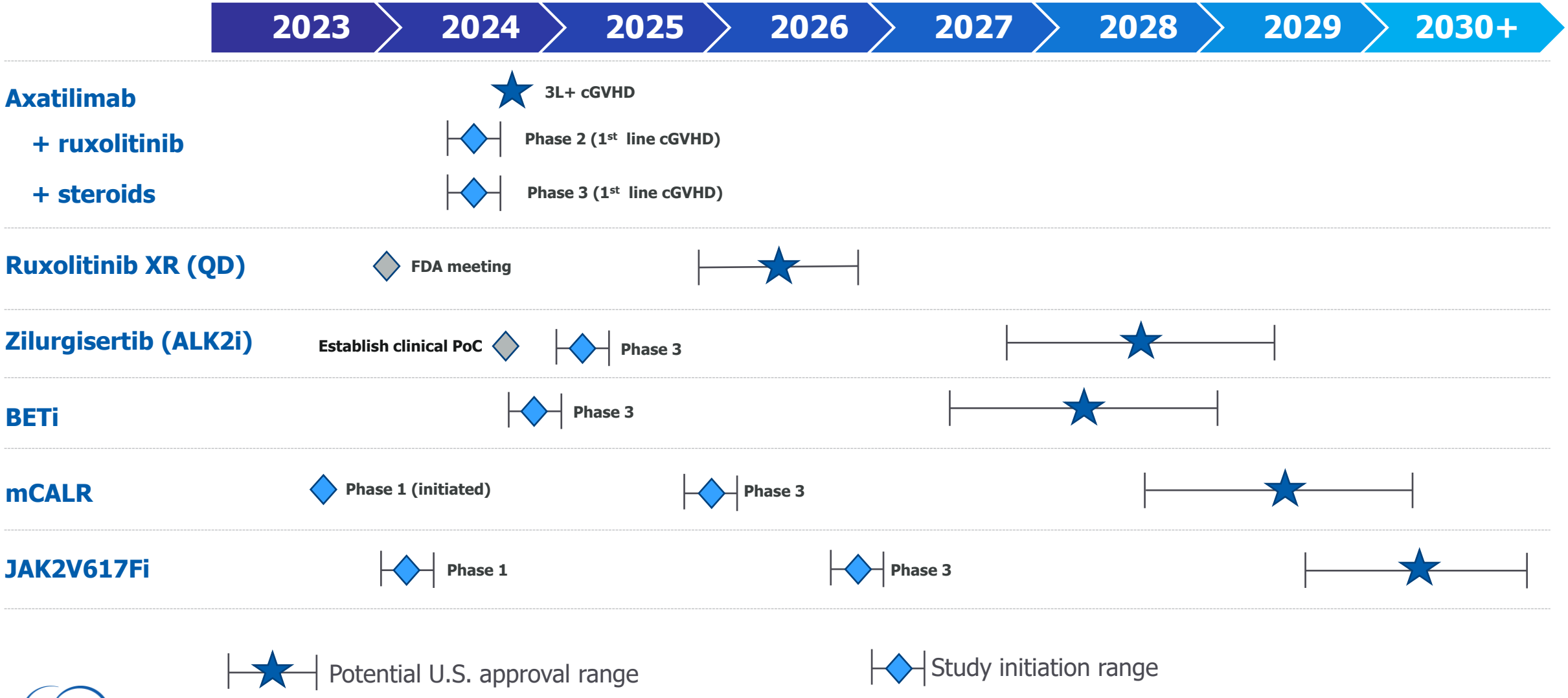
- Preliminary FDA feedback received in December 2023
- Based on feedback from FDA, a PK bridging study with new tablet size with an objective of showing equivalence on both $Cmin_{ss}$ and AUC_{tau} of ruxolitinib will be conducted
- Approval anticipated in ~ 2 years
- Provides simplified dosing strategy and fixed-dose combination advantages with potential for substantial benefit for patients
  - i.e. BET, ALK2 and potentially JAK2V617F

Potential to Expand Axatilimab Opportunity in cGVHD to Earlier Lines of Therapy



1. Flowers M, Storer B, Carpenter P et al. Treatment change as a predictor of outcome among patients with classic chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2008 December; 14 (12): 1380-1384. 2. Incyte data on file

Anticipated Portfolio Timelines and Milestones



ROSS LEVINE, M.D.

DEPUTY PHYSICIAN-IN-CHIEF, TRANSLATIONAL RESEARCH

MEMORIAL SLOAN KETTERING CANCER CENTER

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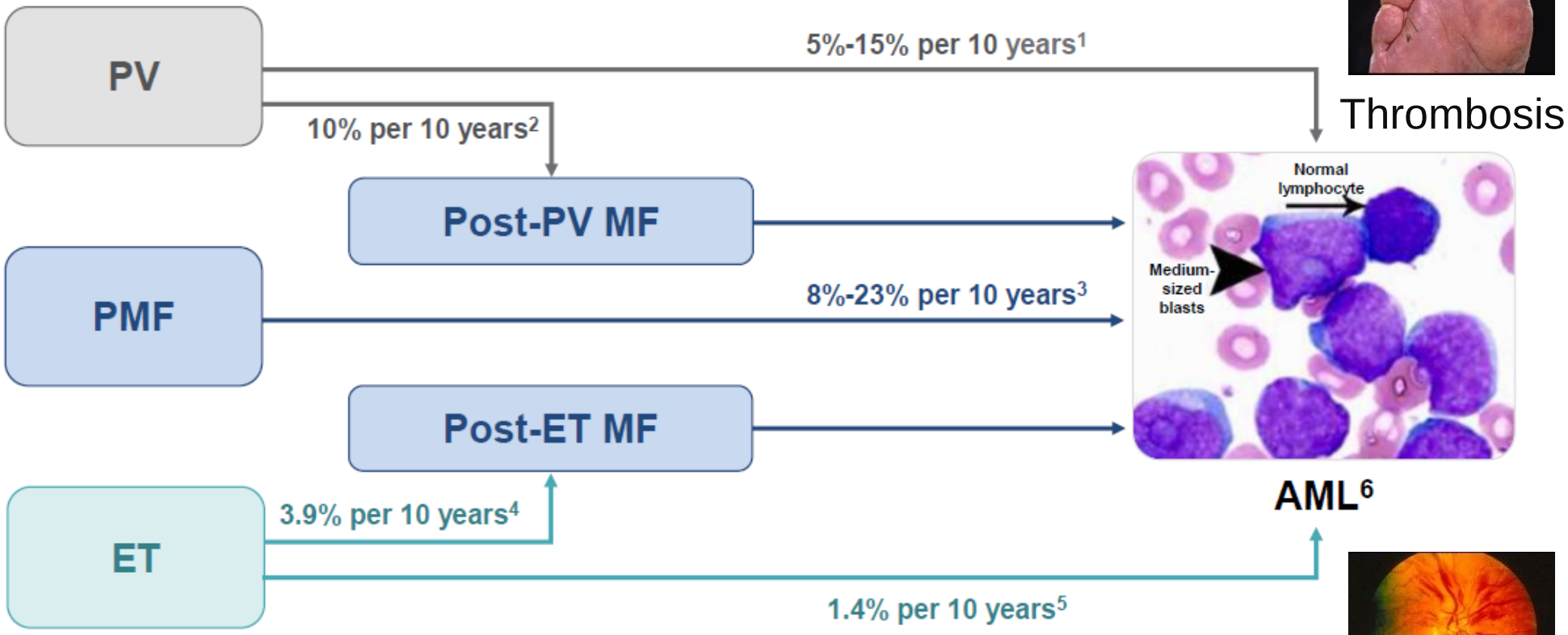
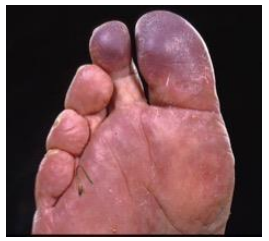
MPN Disease Progression and Transformation

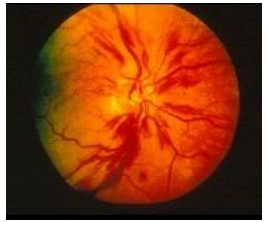
William Dameshek

1951





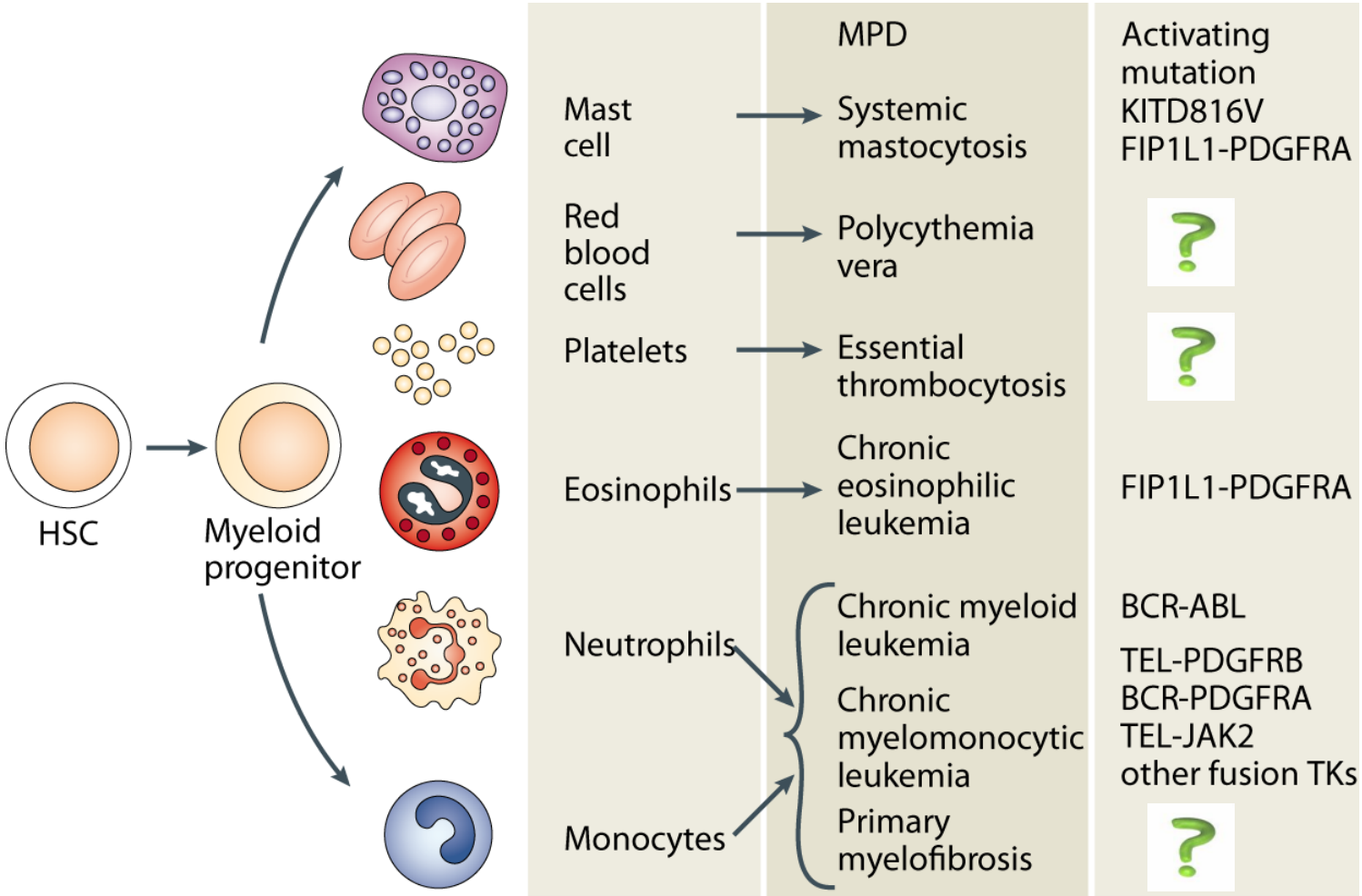
Thrombosis



Hemorrhage

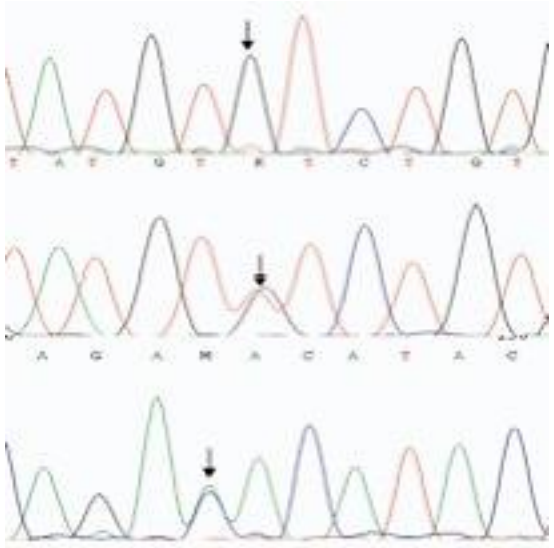
AML, acute myeloid leukemia; PMF, primary myelofibrosis. 1. Finazzi G, et al. *Blood*. 2005;105:2664-2670. 2. Tefferi A. *Am J Hematol*. 2008;83:491-497. 3. Mesa RA, et al. *Blood*. 2005;105:973-977. 4. Cerquozzi S, Tefferi A. *Blood Cancer J*. 2015;5:e366. 5. Wolanskyj AP, et al. *Mayo Clin Proc*. 2006;81:159-166. 6. Reproduced with permission from Pathpedia. AML-M0, blood. Accessed Aug 2022. www.pathpedia.com/education/eatlas/histopathology/blood_cells/aml-m0_blood.aspx.

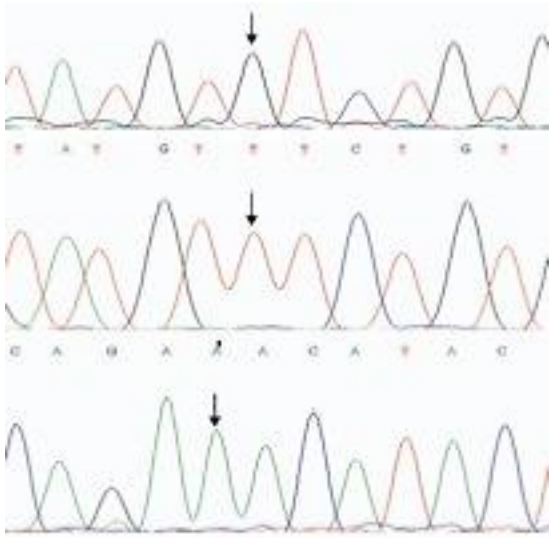
Myeloproliferative Disorders: 2004
Goal: Find the Mutant Gene…



Nature Reviews | Cancer

JAK2V617F Mutations in PV, ET, and MF*





JAK2 - Wildtype

DNA	tat	gga	gta	tgt	gtc	tgt	gga	gac
Protein	Y	G	V	C	V	C	G	D

617

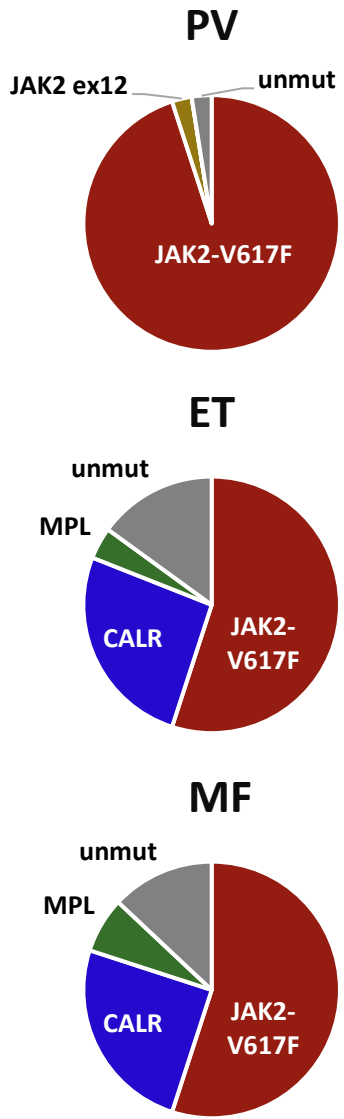
JAK2 - Mutant

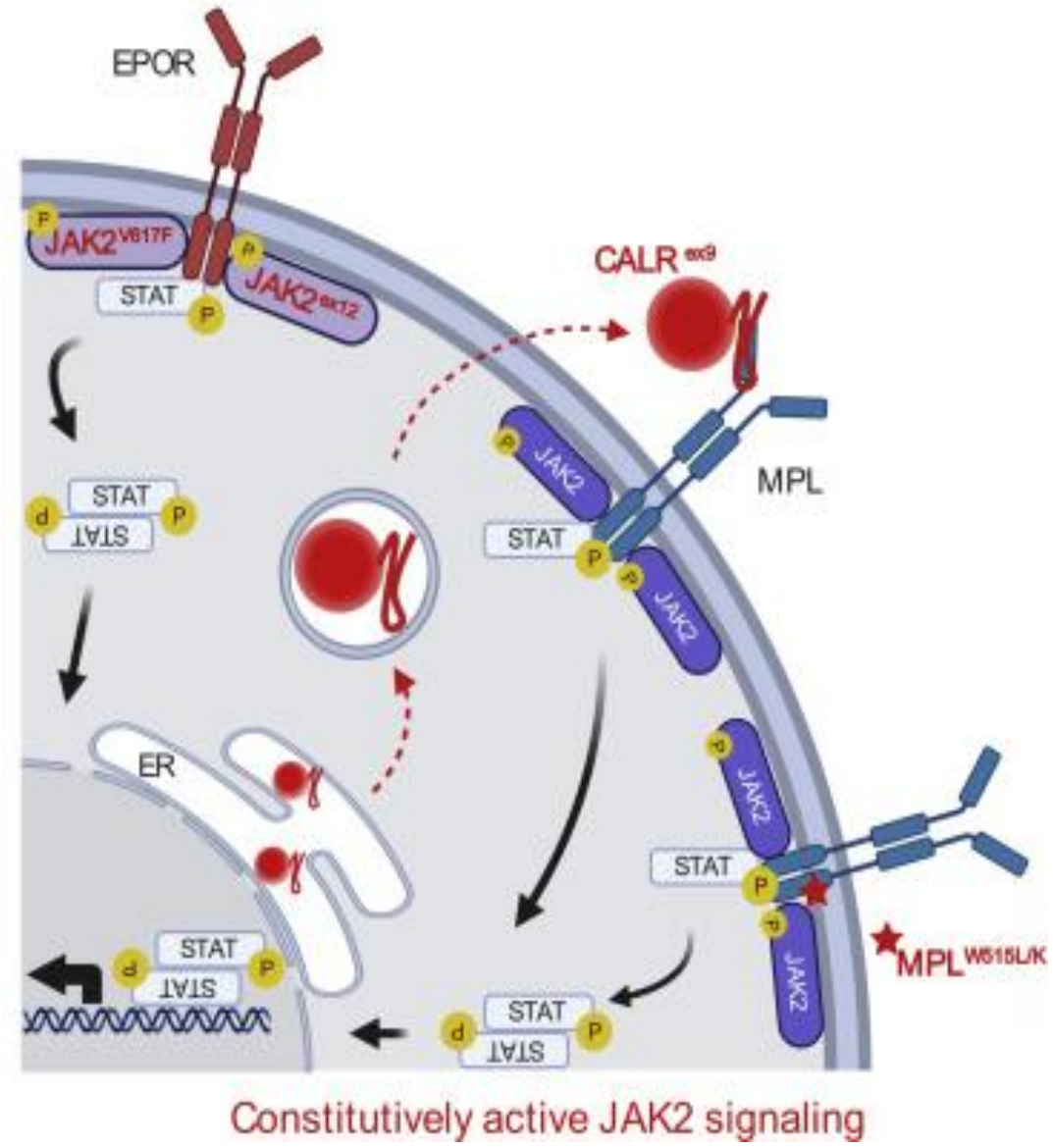
	tat	gga	gta	tgt	ttc	tgt	gga	gac
	Y	G	V	C	F	C	G	D

617

*James *et al.* Nature 2005
Levine *et al.* Cancer Cell 2005
Baxter *et al.* Lancet 2005
Kralovics *et al.* NEJM 2005

JAK-STAT Pathway Remains the Best Therapeutic Target in MPN

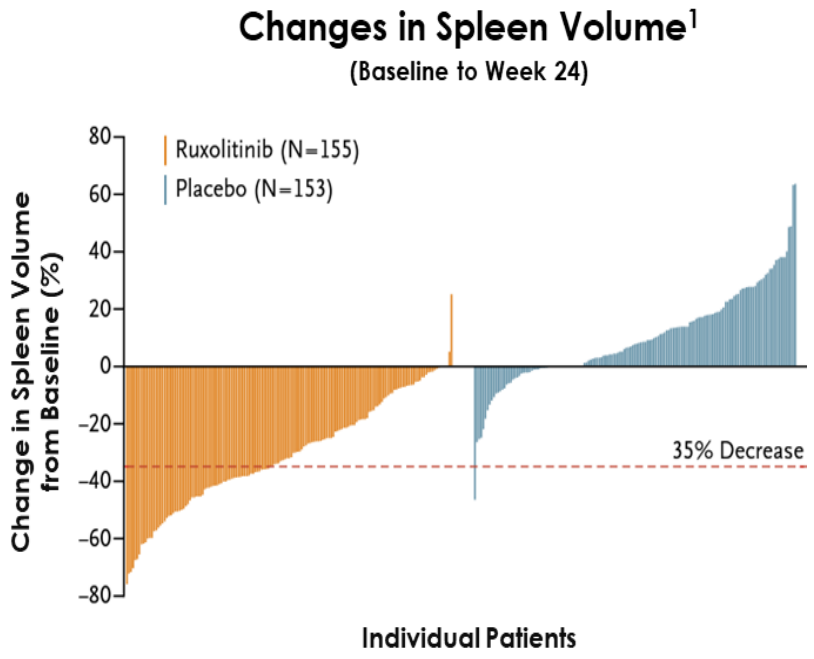


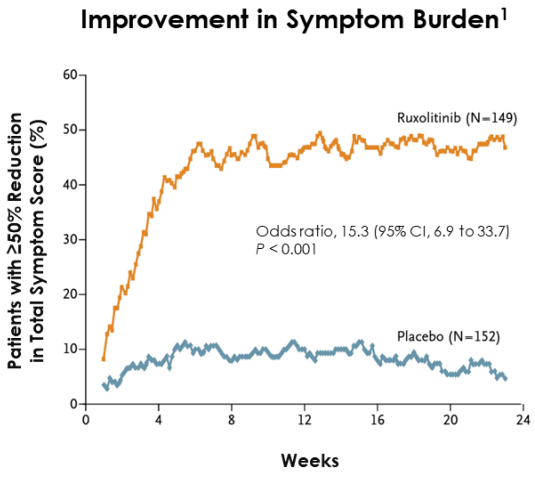


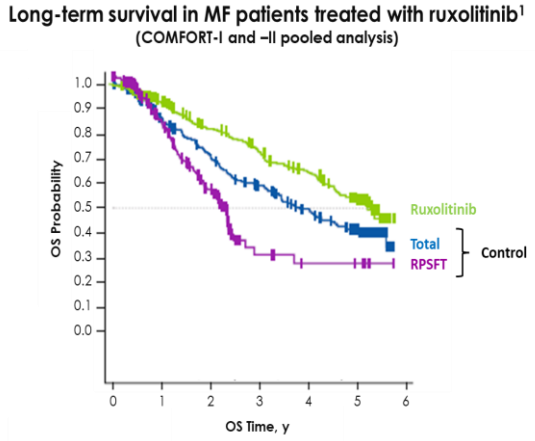
- JAK2 mutations are the most common →best therapeutic target
- Gene expression studies suggest JAK-STAT pathway activated in all MPN patients
- Relevance of clonal evolution/ sequential mutation acquisition to clinical outcome/ therapeutic response not known

Szybinski et al. Hematology/Oncology Clinics 2021

COMFORT I Trial: Spleen Volume Reduction with Ruxolitinib vs. Placebo



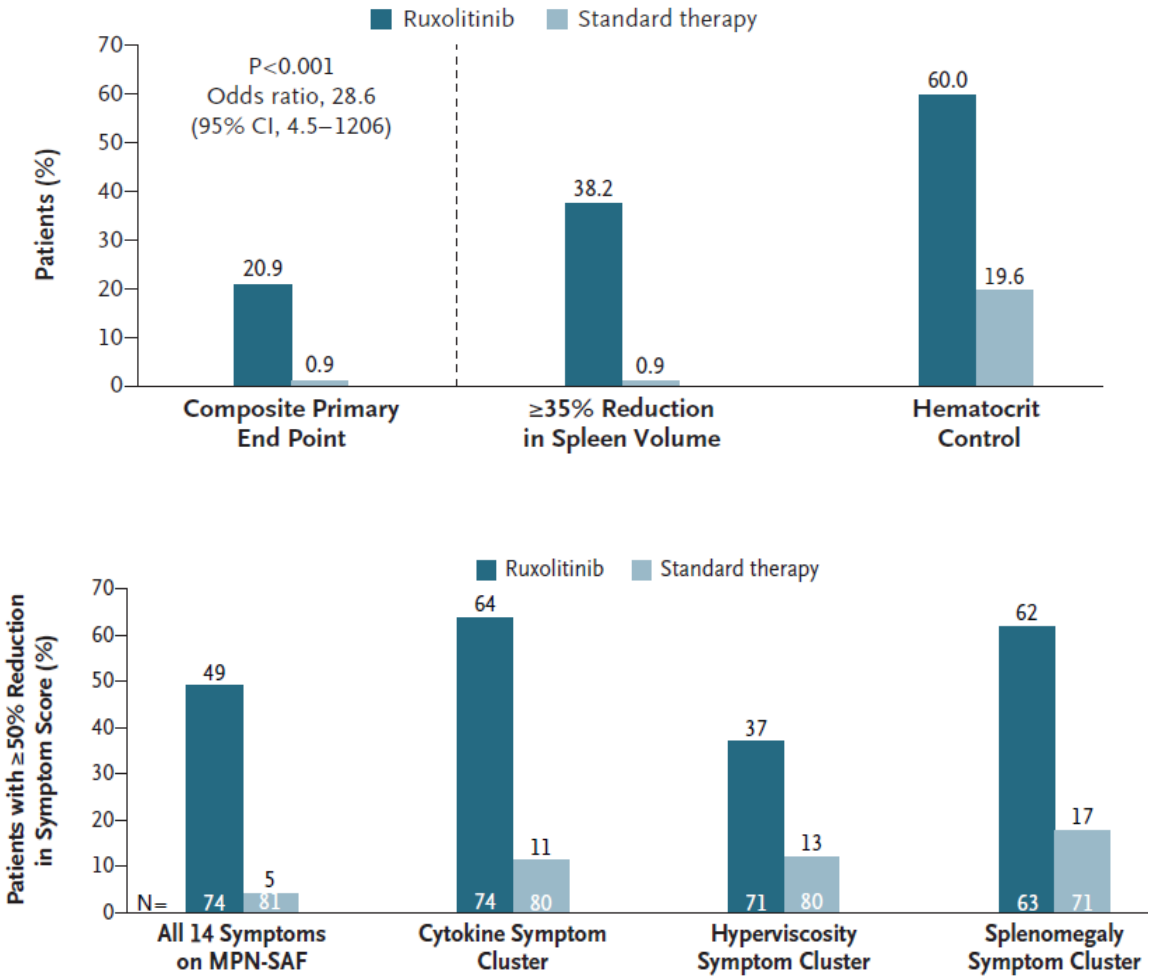




- Ruxolitinib changed the standard of care for MF → first therapy to show true clinical benefit in first-line MF
- The role of other clinical JAK inhibitors remains relatively limited to specific subsets/ second line use
- There remains a need to build on the success of ruxolitinib to further improve outcomes for MPN patients

1. Verstovsek et al. NEJM 2011

RESPONSE Trial: Spleen Volume Reduction and Hematocrit Control with Ruxolitinib vs. Placebo



- Ruxolitinib changed the standard of care for PV → first therapy to show true clinical benefit after HU failure
- Substantial reduction in spleen volume and hematocrit control → hematocrit control associated with reduced risk of death
- Improvements across all MPN related symptoms

Vannucchi et al. NEJM 2015

Entering a New Era of Drug Development in MPNs

- Are there additional targets/ pathways which contribute to MPN pathogenesis/ progression?
  - Can they be used as part of combination strategies which potentiate JAK kinase inhibition?
  - Is there a role for targeting other pathways as monotherapy in MPNs?

- Can we build on the success of current JAK kinase inhibitors to develop better JAK-STAT targeting therapies for MPN patients?
  - More potent/mutant-selective therapies for MPN subtypes (JAK2V617F, MPL, CALR)?

Combination Therapies for MPN Patients

- There are compelling preclinical->clinical data suggesting that specific therapies might potentiate JAK inhibition in MF
  - **BRD4**
  - **BCL2/ BCL-XL**
  - **ALK2**

- Ruxolitinib is the combination “backbone” for most of these studies → represents an excellent combination therapy partner

Combination Therapies for MPN Patients Continued

- Beginning to see data from large combination therapy trials in the MF first/ second line
  - Primary efficacy readouts → spleen response, symptoms
    - *Does combination therapy need to show superiority over JAK inhibitor monotherapy for both spleen and symptom response to gain approval?*
  - Secondary readouts of efficacy (fibrosis, progression, mutant allele burden) will be key
  - Toxicity/ dose-modification will be critical to assess, especially given that both BRD4 and BCL-XL inhibition have on-target thrombocytopenia
  - Will there be specific subsets where combination therapy is most effective?

- Ruxolitinib monotherapy likely to remain as the preferred therapy of choice for most 1L MF and 2L PV patients

Novel JAK-STAT Targeting Therapies

- Although current JAK inhibitors offer significant benefit to MPN patients, they cannot fully inhibit mutant-driven aberrant JAK2 signaling

- As such there remains a need to develop new therapeutic modalities which directly and specifically inhibit driver mutations in MPNs
  - **Mutant MPL**
  - **Mutant CALR**
  - **JAK2V617F**

- mCALR-targeting antibodies have the potential to be a highly efficacious, mutant-selective therapy for CALR-mutant ET and MF

- JAK2V617F-selective therapies could represent the best-in-class future therapy for JAK2V617F-mutant PV, ET, and MF
  - Mutant selectivity should allow for greater inhibition of aberrant pathway activation without targeting JAK2 signaling in non-mutant hematopoietic cells

JOHN MASCARENHAS, M.D.

PROFESSOR OF MEDICINE, DIRECTOR OF THE ADULT LEUKEMIA PROGRAM

THE TISCH CANCER INSTITUTE AT MOUNT SINAI

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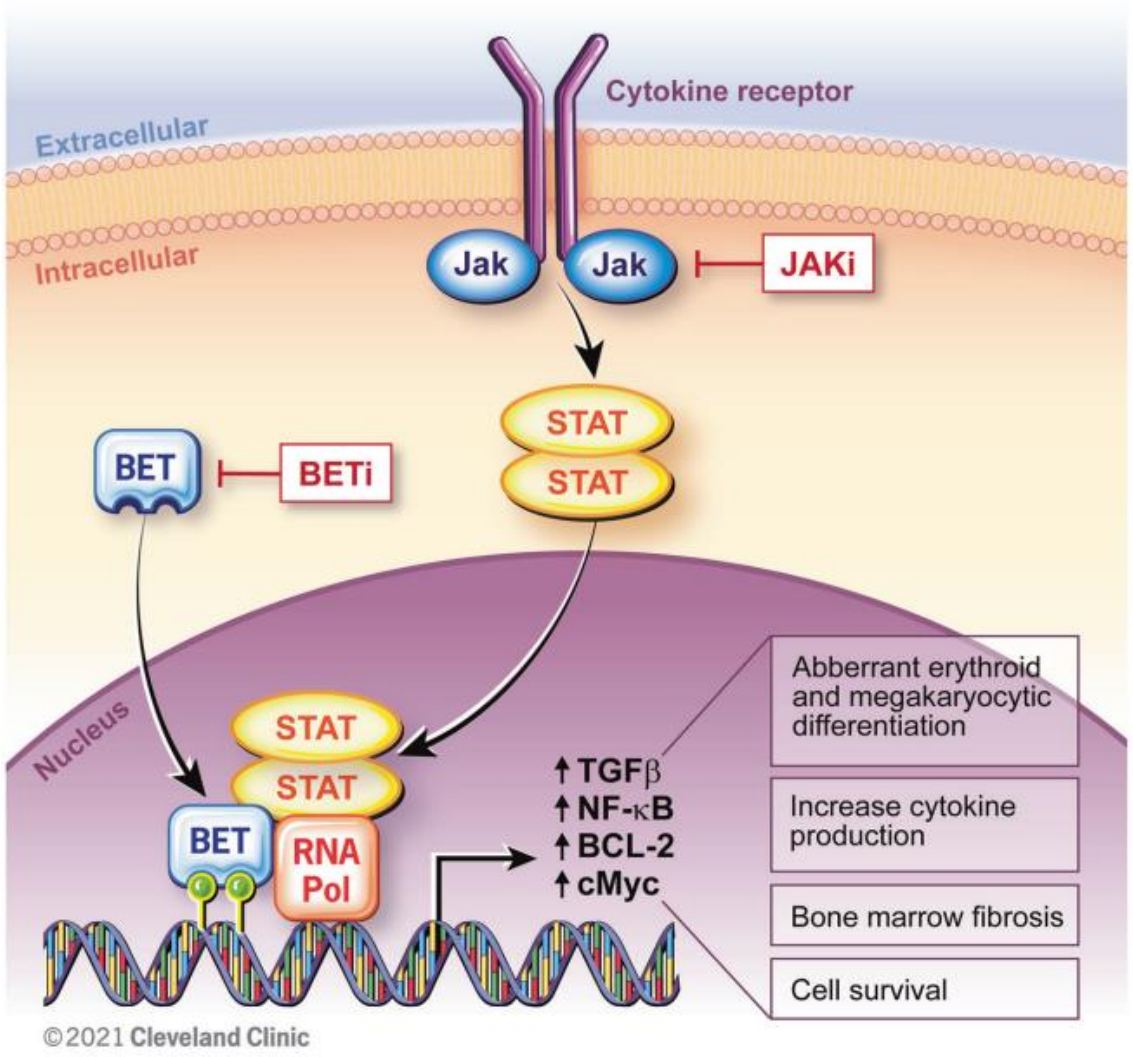
INCB57643 (BETi) ± RUXOLITINIB

INCB57643 (BETi) ± Ruxolitinib Overview

- ✓ **Improvements in spleen size and symptom burden** have been observed
- ✓ INCB57643 monotherapy or in combination with ruxolitinib was **generally well tolerated**

- Plan to open **Phase 3 study in 2H 2024**
  - Potential in the first-line, suboptimal or as monotherapy after ruxolitinib failures
  - Patient population details to be studied in Phase 3 will be disclosed in the coming months

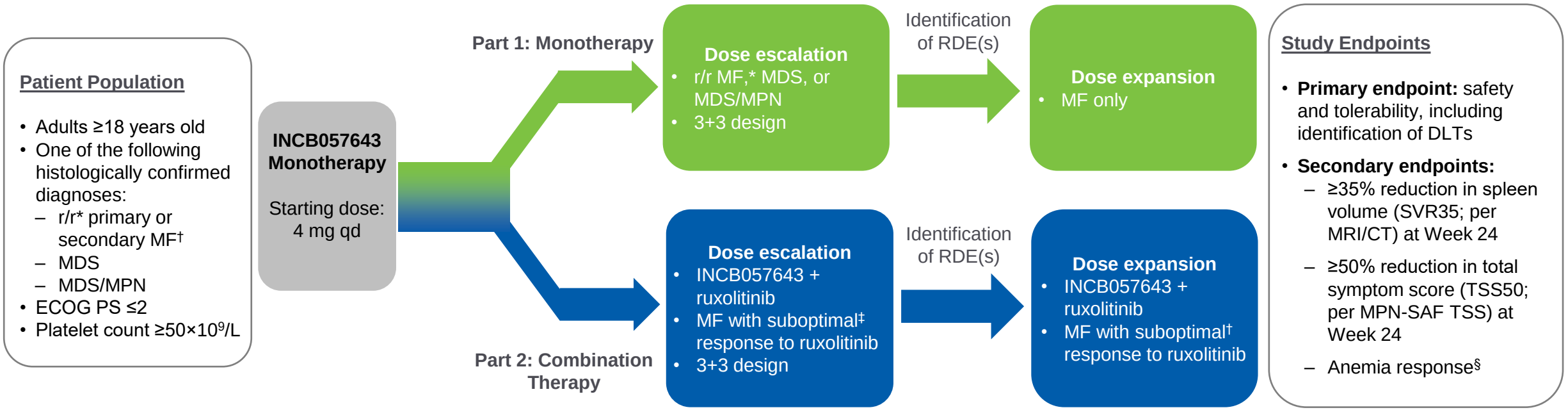
JAKi and BETi Cooperate to Inhibit NFkB And Downregulate Target Gene Expression



Mascarenhas J, et al. Leukemia. 2021;35:3361-3363

BETi Phase I Dose-Escalation and Dose-Expansion Study Design

- The initial INCB057643 dose was 4 mg qd with dose escalation up to 12 mg qd
  - All doses were administered continuously in 28-day cycles



DLT= dose-limiting toxicity; ECOG PS= Eastern Cooperative Oncology Group performance status; MDS= myelodysplastic syndromes; MF= myelofibrosis; MPN= myeloproliferative neoplasm; qd= once daily; RDE= recommended doses for expansion; r/r= relapsed/refractory; SAF TSS= Symptom Assessment Form Total Symptom Score.

* Patients who have received ≥1 line of prior therapy and experienced a recurrence of their disease or failed to respond to the last treatment, and for whom no additional known therapy is available to offer clinical benefits. † Patients with MF must have received a Janus kinase inhibitor(s) such as ruxolitinib. ‡ Patients who have been receiving a stable dose of ruxolitinib 5 to 25 mg twice daily for at least 8 weeks prior to the first dose of study treatment (INCB057643 4 mg or 6 mg) but are not experiencing an optimal response to ruxolitinib monotherapy. § Defined as a hemoglobin increase of ≥1.5 g/dL from baseline lasting ≥12 weeks during the treatment period if transfusion-independent at baseline OR achieving transfusion independence for ≥12 weeks during the treatment period if transfusion-dependent at baseline.

Patient Demographics and Baseline Characteristics

Parameter	INCB057643 Monotherapy (n=18)	INCB057643 + RUX (n=11)
Age, median (range), y	70.0 (50–79)	70.0 (50–76)
Male, n (%)	11 (61.1)	6 (54.5)
White, n (%)	14 (77.8)	10 (90.9)
Malignancy type, n (%)		
MF	13 (72.2)	11 (100.0)
DIPSS Int-2	12/13 (92.3)	10 (90.9)
DIPSS high risk	1/13 (7.7)	0
MF risk missing	0	1 (9.1)
Primary MF	4/13 (30.8)	5 (45.5)
Post-PV-MF	5/13 (38.5)	2 (18.2)
Post-ET-MF	4/13 (30.8)	4 (36.4)
CMML	2 (11.1)	0
MDS	1 (5.6)	0
MDS/MPN-RS-T	1 (5.6)	0
Unclassifiable MDS/MPN overlap syndrome	1 (5.6)	0

Parameter	INCB057643 Monotherapy (n=18)	INCB057643 + RUX (n=11)
ECOG PS, n (%)		
0	2 (11.1)	6 (54.5)
1	16 (88.9)	4 (36.4)
2	0	1 (9.1)
JAK2-positive [among MF patients], n (%)	9/13 (69.2)	8/11 (72.7)
RBC transfusion dependent, n (%)		
Yes	2 (11.1)	0
No	16 (88.9)	11 (100.0)
Prior treatment, n (%)		
Systemic therapy	17 (94.4)	11 (100.0)
Radiotherapy	2 (11.1)	0
Stem cell transplant	0	0
Spleen volume,* median (range), mL	2028.0 (618–4766)	1747.0 (702–4381)
MPN-SAF TSS,† median (range)	32.0 (0–78)	23.0 (2–43)

CMML= chronic myelomonocytic leukemia; DIPSS= Dynamic International Prognostic Scoring System; ECOG PS= Eastern Cooperative Oncology Group performance status; Int= intermediate; MDS,= myelodysplastic syndromes; MF= myelofibrosis; MPN= myeloproliferative neoplasm; post–ET-MF= post–essential thrombocythemia myelofibrosis; post–PV-MF= post–polycythemia vera myelofibrosis; RBC= red blood cell; RS-T= ring sideroblasts and thrombocytosis; RUX= ruxolitinib; SAF TSS= Symptom Assessment Form total symptom score.

* Among evaluable patients with MF: 4-mg cohort, n=4; 6-mg cohort, n=1; 8-mg cohort, n=3; 10-mg cohort, n=4; 12-mg cohort, n=1; 4-mg + RUX cohort, n=5; 6-mg + RUX cohort, n=6.

† Among patients with baseline MPN-SAF assessment: 4-mg cohort, n=3; 6-mg cohort, n=1; 8-mg cohort, n=3; 10-mg cohort, n=4; 12-mg cohort, n=1; 4-mg + RUX cohort, n=5; 6-mg + RUX cohort, n=5.

Safety

- Grade ≥3 TEAEs occurred in 65.5% and serious TEAEs in 20.7% of patients
- There were 2 DLTs with monotherapy and 1 DLT with combination therapy
  - Hyperbilirubinemia (MF patient, 12-mg cohort)
  - Thrombocytopenia (MDS/MPN patient, 12-mg cohort; MF patient, 6 mg + ruxolitinib cohort)

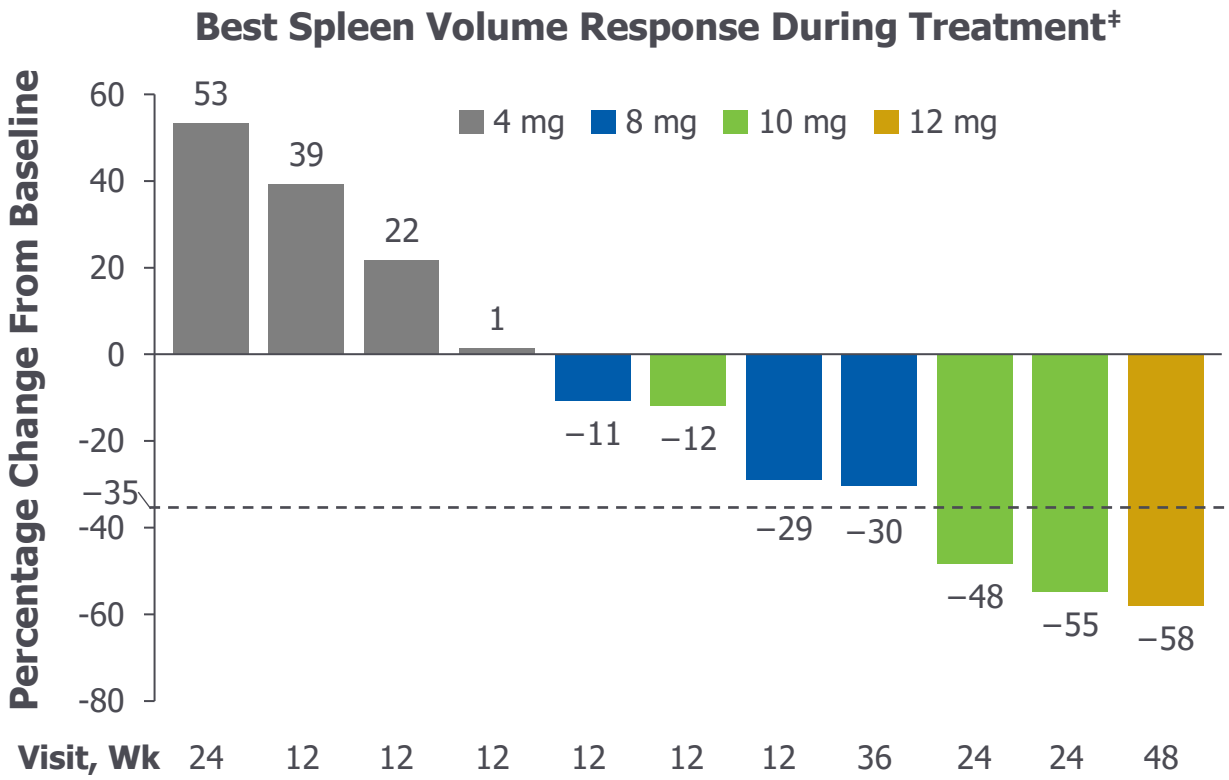
	INCB057643 Monotherapy (n=18)	INCB057643 + RUX (n=11)	Total (N=29)
Any TEAE	18 (100.0)	11 (100.0)	29 (100.0)
Grade 3 TEAE*	13 (72.2)	6 (54.5)	19 (65.5)
TEAE leading to discontinuation†	4 (22.2)	1 (9.1)	5 (17.2)
Serious TEAE	5 (27.8)	1 (9.1)	6 (20.7)
Fatal TEAE‡	1 (5.6)	0	1 (3.4)
Treatment-related TEAE	17 (94.4)	7 (63.6)	24 (82.8)
Treatment-related serious TEAE§	1 (5.6)	0	1 (3.4)

	INCB057643 Monotherapy (n=18)	INCB057643 + RUX (n=11)	Total (N=29)
Most common TEAEs, n (%)¶			
Thrombocytopenia	8 (44.4)	7 (63.6)	15 (51.7)
Nausea	8 (44.4)	0	8 (27.6)
Anemia	6 (33.3)	2 (18.2)	8 (27.6)
Blood bilirubin increased	6 (33.3)	2 (18.2)	8 (27.6)
Hyperuricemia	6 (33.3)	0	6 (20.7)
Dysgeusia	5 (27.8)	1 (9.1)	6 (20.7)
Blood creatinine increased	3 (16.7)	3 (27.3)	6 (20.7)

RUX= ruxolitinib; TEAE= treatment-emergent adverse event.
* Grade ≥3 TEAEs occurring in ≥2 patients: anemia (n=6), thrombocytopenia (n=8), hypokalemia (n=2), platelet count decreased (n=2). † TEAEs leading to discontinuation of INCB057643: thrombocytopenia (n=4), anemia (n=1), and bacteremia (n=1). ‡ Fatal TEAE: transformation to acute myeloid leukemia (n=1). § Treatment-related serious TEAE: pneumonia (n=1). ¶TEAEs occurring in ≥20% of patients in the total population.

Monotherapy with BETi Demonstrates Spleen Volume Responses

- At Week 24, SVR35 was achieved by 3 patients receiving INCB057643 ≥10 mg
- 5 patients treated at any dose achieved best response of ≥25% reduction in spleen volume during the treatment period

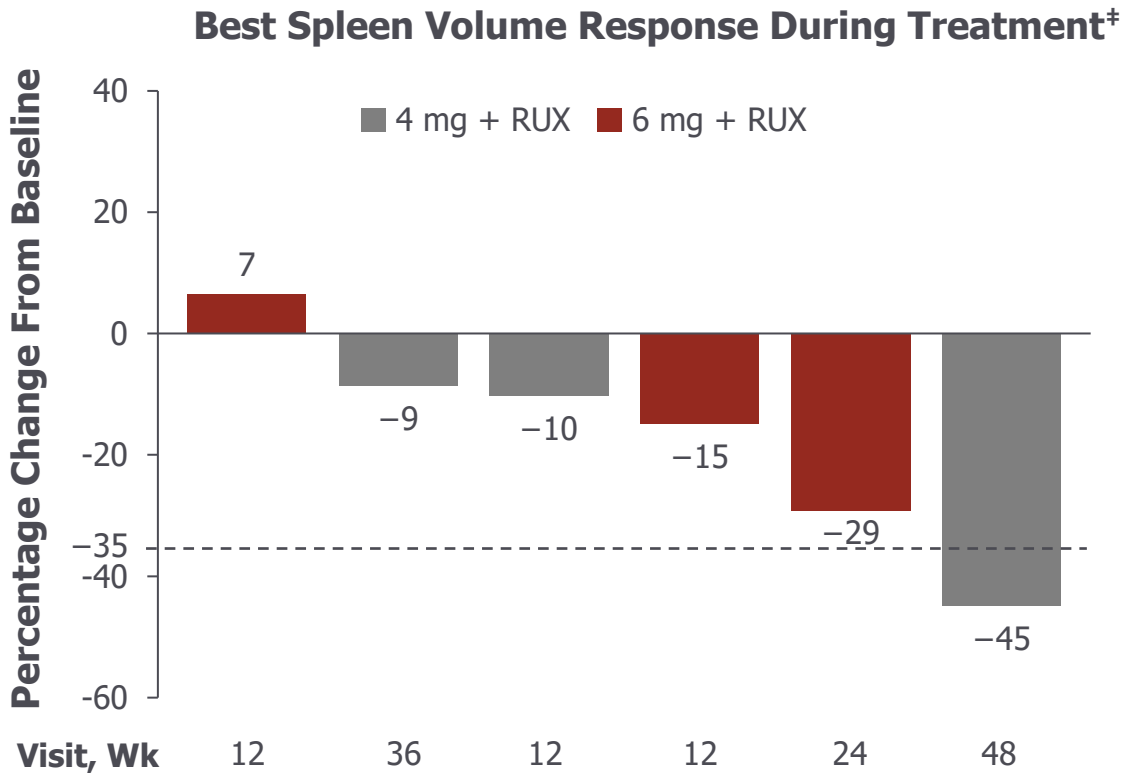


MF= myelofibrosis; SVR35= 35% reduction from baseline in spleen volume

* Dotted line represents response criteria threshold. † 4 evaluable patients receiving monotherapy (4-mg, n=3 and 6-mg, n=1) discontinued from treatment before Week 24; 2 patients receiving ongoing 10-mg monotherapy were not evaluable because they were not followed up long enough and had no Week 24 assessment. ‡ 1 evaluable patient receiving 6-mg monotherapy discontinued from treatment before first post-baseline (Week 12) spleen volume assessment; 1 patient receiving ongoing 10-mg monotherapy was not evaluable because they were not followed up long enough and had no Week 12 spleen volume assessment.

BETi in Combination with Ruxolitinib Demonstrates Spleen Volume Responses

- At Week 24, SVR35 was achieved by 1 patient receiving INCB057643 4 mg + ruxolitinib
- Improvements in spleen volume were observed in 5 patients, with 2 achieving best response of ≥25% reduction in spleen volume during the treatment period

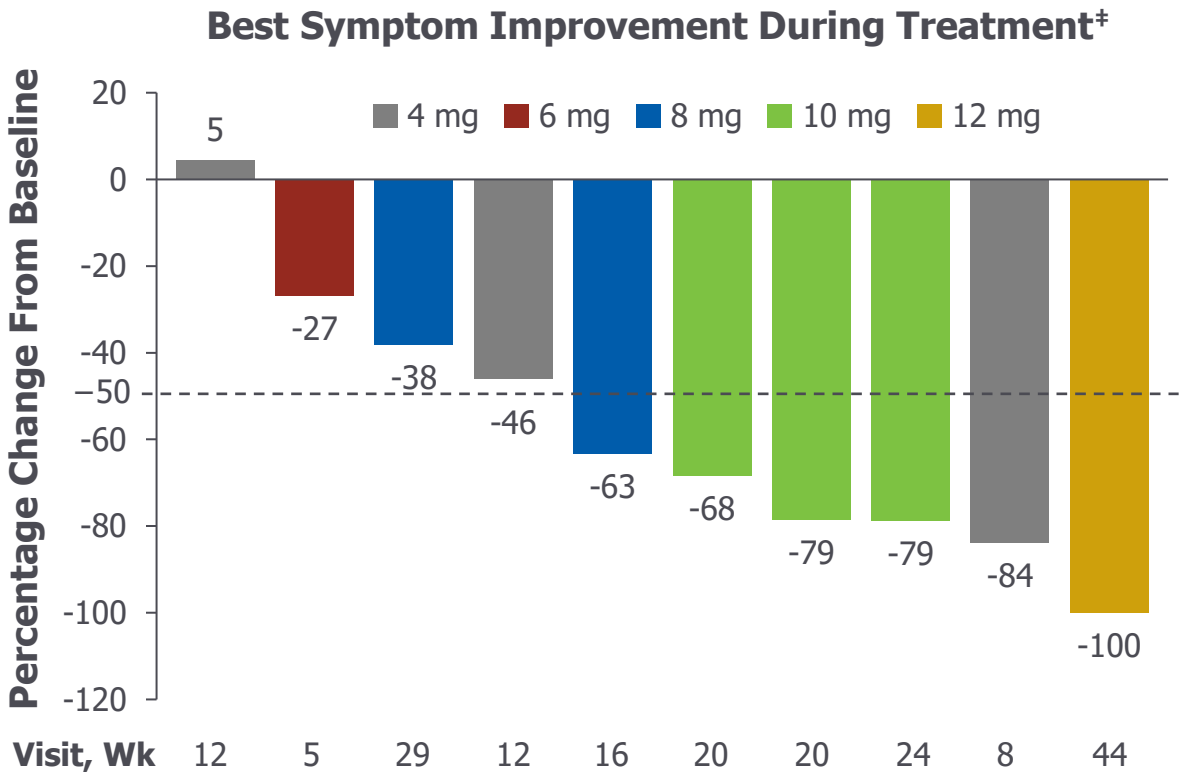


MF= myelofibrosis; RUX= ruxolitinib; SVR35= 35% reduction from baseline in spleen volume

* Dotted line represents response criteria threshold. † 1 evaluable patient receiving 4-mg + RUX discontinued from treatment before Week 24; 2 patients receiving ongoing 4-mg + RUX and 4 patients receiving ongoing 6-mg + RUX were not evaluable because they were not followed up long enough and had no Week 24 assessment or did not have a Week 24 assessment at the time of data extraction. ‡ 1 evaluable patient receiving 4-mg + RUX discontinued from treatment before first post-baseline (Week 12) spleen volume assessment; 1 patient receiving ongoing 4-mg + RUX and 3 receiving ongoing 6-mg + RUX were not evaluable because they were not followed up long enough and had no Week 12 spleen volume assessment.

BETi Monotherapy Led to Symptom Improvements[1]

- At Week 24, TSS50 was achieved by 3 patients receiving INCB057643 ≥10 mg
- 6 patients treated at any dose achieved best response of ≥50% improvement in symptom score during the treatment period



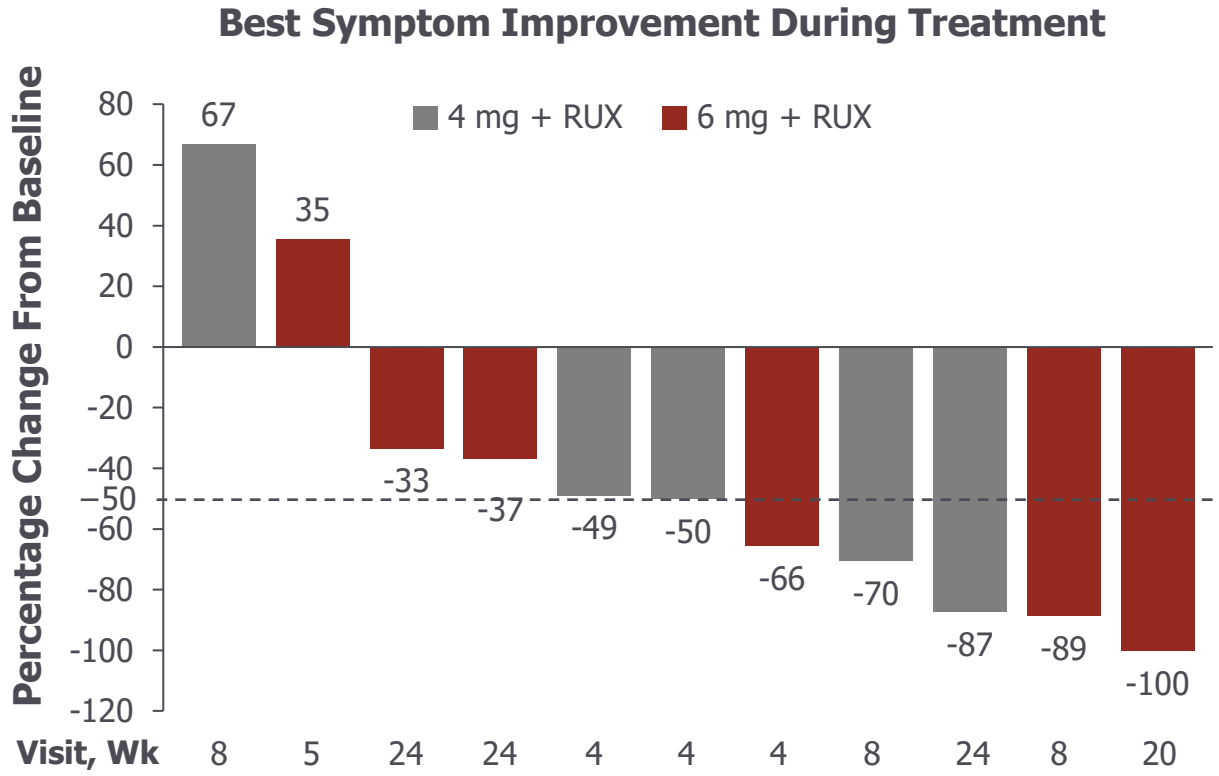
1. Measured by MPN-SAF TSS

MF= myelofibrosis; MPN-SAF TSS= myeloproliferative neoplasm-Symptom Assessment Form Total Symptom Score; TSS50= ≥50% reduction from baseline in MPN-SAF TSS

* Dotted line represents response criteria threshold. † 4 evaluable patients receiving monotherapy (4-mg, n=3 and 6-mg, n=1) discontinued from treatment before Week 24; 3 patients receiving monotherapy were not evaluable because baseline assessment was missing (4-mg, n=1 and 8-mg, n=1) or they were ongoing but not followed up long enough and had no Week 24 assessment (10-mg, n=1). ‡ 3 patients receiving monotherapy were not evaluable, 2 patients (4-mg, n=1 and 8-mg, n=1) did not have baseline assessment and 1 receiving 10-mg monotherapy did not have post-baseline MPN-SAF TSS assessment.

Symptom Improvements with BETi in Combination with Ruxolitinib

- At Week 24, TSS50 was achieved by 2 patients (1 in each cohort)
- 6 patients treated at any dose achieved best response of ≥50% improvement in symptom score during the treatment period



MF= myelofibrosis; MPN-SAF TSS= myeloproliferative neoplasm-Symptom Assessment Form Total Symptom Score; RUX= ruxolitinib; TSS50= ≥50% reduction from baseline in MPN-SAF TSS

* Dotted line represents response criteria threshold. † 1 evaluable patient receiving 4-mg + RUX discontinued from treatment before Week 24; 5 patients were not evaluable because baseline assessment was missing (6-mg + RUX, n=1) or they were ongoing but not followed up long enough and had no Week 24 assessment (4-mg + RUX, n=2 and 6-mg + RUX, n=3).

BETi ± Ruxolitinib: Conclusions and Next Steps

- ✓ Improvements in spleen size and symptom burden were observed with INCB57643 ≥ 8mg QD monotherapy and 4mg and 6mg combination therapy
- ✓ INCB57643 monotherapy or in combination with ruxolitinib was generally well tolerated
- ✓ Dose escalation complete for INCB57643 monotherapy with 6mg and 10mg identified as recommended doses for expansion
- ✓ Dose escalation is ongoing in the combination therapy group; currently enrolling in the 8mg cohort

Next Steps

- Plan to open Phase 3 in 2H 2024
  - Potential in the first-line, suboptimal or as monotherapy after ruxolitinib failures
  - Patient population details to be studied in Phase 3 will be disclosed in the coming months

ZILURGISERTIB (ALK2I) ± RUXOLITINIB

Zilurgisertib (ALK2i) ± Ruxolitinib: Overview

- ✓ Goal of program is to **prevent / reduce anemia** while maintaining optimal dose intensity of ruxolitinib
- ✓ **Hepcidin reduction** observed
- ✓ Generally safe and well tolerated

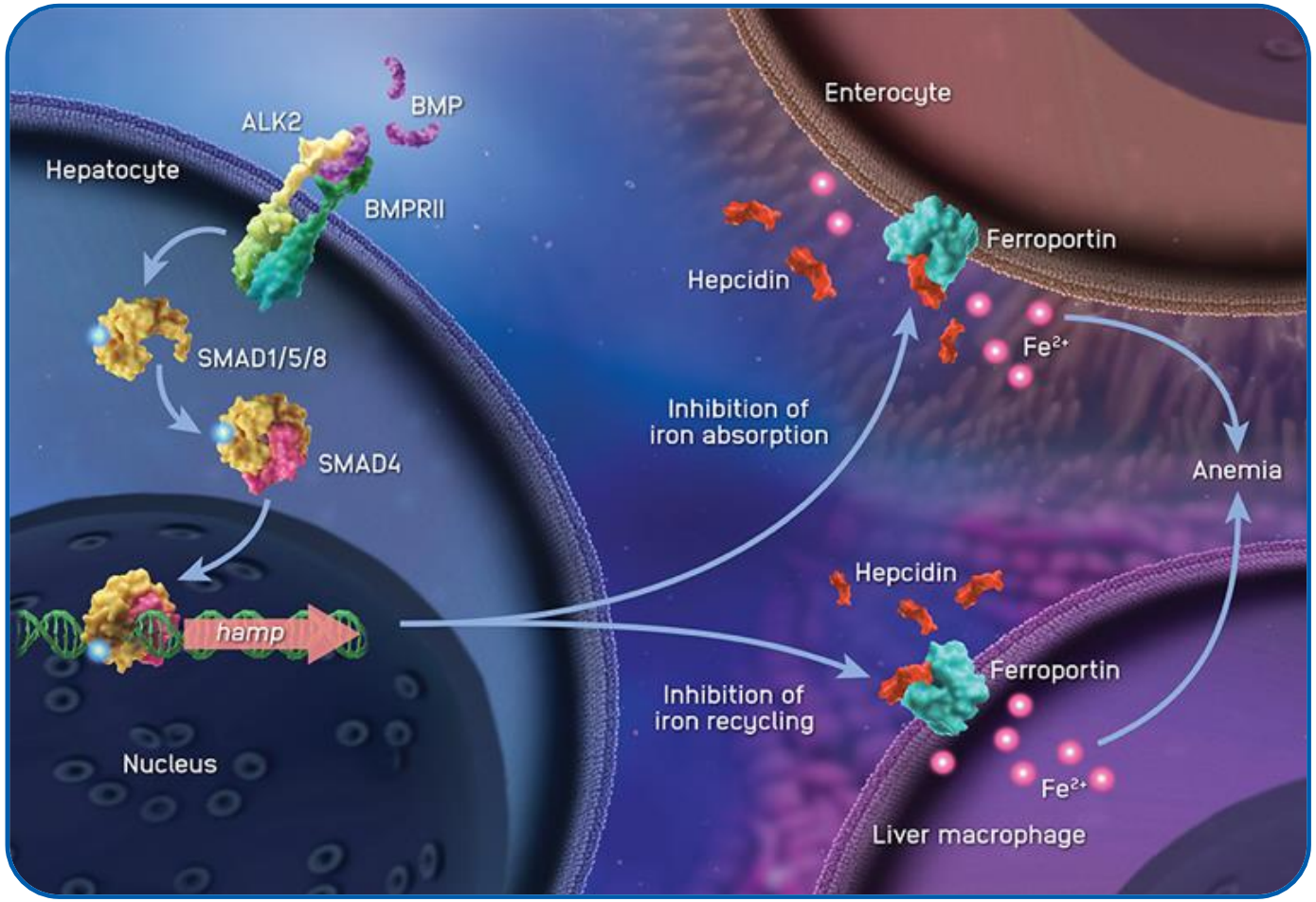
- Next steps
  - Dose escalation continues
  - Clinical **proof-of-concept** anticipated by **mid-2024**

ALK2 Mechanism of Action: Potential to Target Hepcidin and Improve Anemia

Zilurgisertib (ALK2i)
+
Ruxolitinib (JAK1/2)

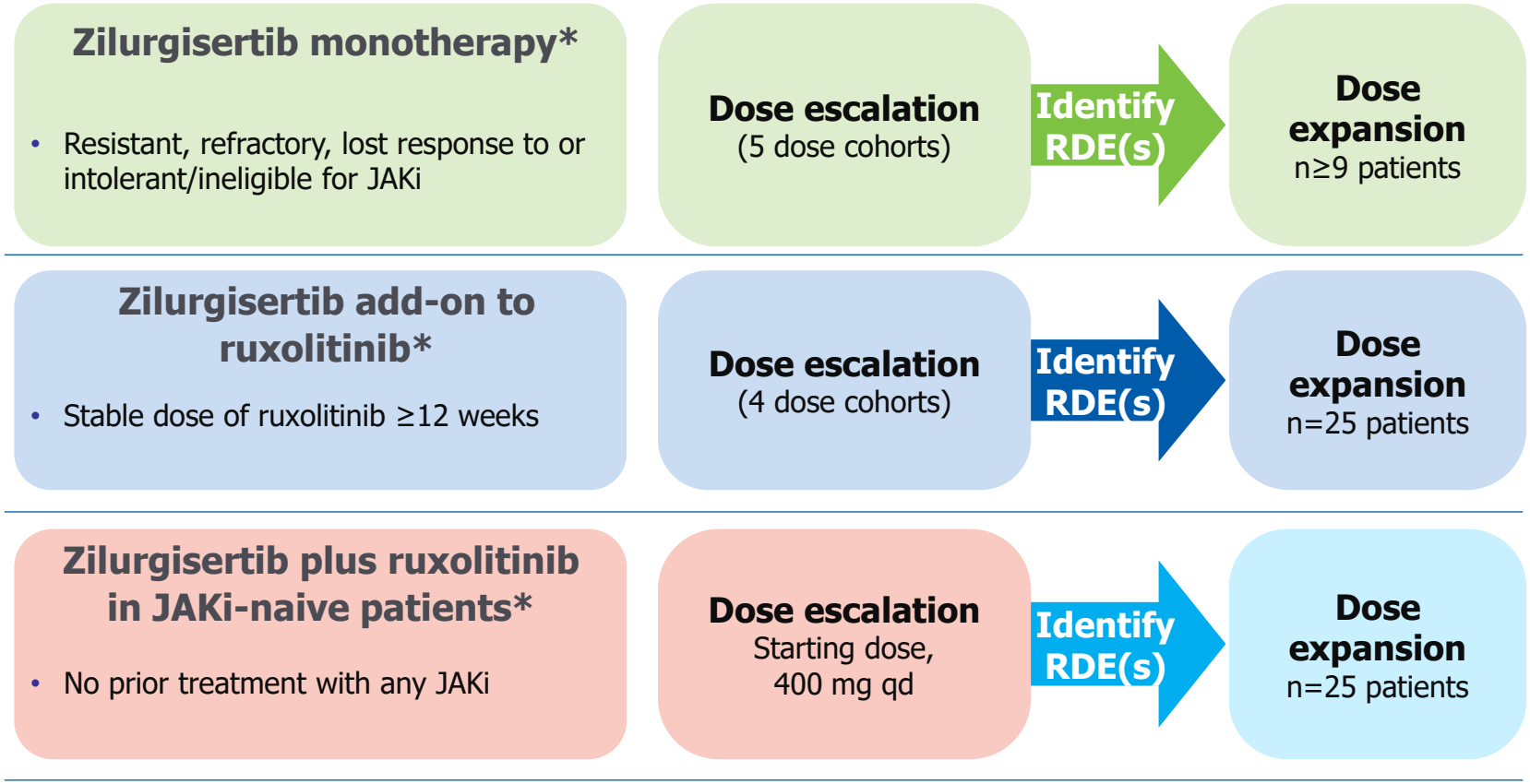
Potential to:

- Alleviate, and/or prevent anemia
- Allow for increased ruxolitinib dose intensity
  - Improves splenomegaly
  - Improves symptoms



1. Pardanani A, et al. Am J Hematol. 2013;88:312-316. 2. Zhou A, et al. Blood 2018;132(Suppl 1):1760. 3. Asshoff M, et al. Blood. 2017;129:1823-1830. 4. Ganz T. Blood. 2011;117:4425-4433. 5. Birgegard G, et al. Eur J Haematol. 2019;102:235-240.

Zilurgisertib Phase 1 Study Design



Primary Endpoint: safety and tolerability of zilurgisertib ± ruxolitinib

Secondary Endpoints: anemia response[1]

Other Secondary Endpoints: PK and pharmacodynamics

****All patients required to have a hgb < 10 g/dL***

1. If non-transfusion dependent at baseline: Hb increase ≥1.5 g/dL relative to baseline for any rolling 12-week period during Weeks 1-24. If transfusion dependent at baseline: achieving transfusion independence for any rolling 12-week period during Weeks 1-24

Zilurgisertib Patient Demographics and Clinical Characteristics

- 46 patients were enrolled at the time of analysis (data cutoff date, August 1, 2023), including 1 in the cohort of zilurgisertib plus ruxolitinib in JAKi-naive patients (data not shown)

	Zilurgisertib Monotherapy (n=23)	Zilurgisertib Add-on to RUX (n=22)
Age, median (range), y	73.0 (53–84)	77.0 (54–85)
Male, n (%)	15 (65.2)	9 (40.9)
Time since MF diagnosis, median (range), y	2.0 (0.2–23.1)	5.5 (0.8–24.1)
Transfusion dependent, n (%)	11 (47.8)	5 (22.7)
DIPSS risk level, n (%)		
High	1 (4.3)	4 (18.2)
Intermediate-2	22 (95.7)	17 (77.3)
Intermediate-1	0	1 (4.5)
Prior MF therapy, n (%)		
Ruxolitinib	14 (60.9)	22 (100.0)
Other JAKi	3 (13.0)	2 (9.1)
Other	9 (39.1)	10 (45.5)
Ruxolitinib starting daily total dose during study, median (range), mg	—	20 (15–50)
Hb, median (range),* g/dL	7.9 (6.5–9.7)	8.0 (5.2–9.1)
Hepcidin, median (range), † ng/mL	202 (18–535)	135 (7–421)

DIPSS= Dynamic International Prognostic Scoring System; Hb= hemoglobin; JAKi= Janus kinase inhibitor; MF= myelofibrosis; qd= once daily; RBC= red blood cell; RUX= ruxolitinib

* Baseline Hb was determined as the average of values obtained during the 3 months prior to C1D1 which met the following criteria: Hb value was obtained outside the 14-day washout period following a RBC transfusion or Hb value triggered a RBC transfusion (even if obtained within the 14-day period following a transfusion). † Normal range, 0–50 ng/mL.

Zilurgisertib Safety

- Dose escalation was ongoing in both treatment groups and MTD had not been reached at the time of analysis
- One dose-limiting toxicity occurred (400 mg add-on therapy, grade 3 alveolar hemorrhage)
- TEAEs were mainly low grade and without apparent dose dependency
- One zilurgisertib-related TEAE led to study drug discontinuation (grade 2 hyperferritinemia; 200 mg add-on therapy)

Zilurgisertib Monotherapy (n=23)		
Event, n (%)	**Any grade**	**Grade ≥3**
Most common TEAE*		
Hyperuricemia	7 (30.4)	0
Nausea	5 (21.7)	0
Pruritus	5 (21.7)	0
Cough	4 (17.4)	0
Dyspnea	4 (17.4)	0
Edema peripheral	4 (17.4)	0
Thrombocytopenia	3 (13.0)	3 (13.0)
COVID-19	3 (13.0)	2 (8.7)
Asthenia	3 (13.0)	0
Constipation	3 (13.0)	0
Decreased appetite	3 (13.0)	0
Diarrhea	3 (13.0)	0
Dysphagia	3 (13.0)	0
Epistaxis	3 (13.0)	0
Fatigue	3 (13.0)	0
Headache	3 (13.0)	0
Myalgia	3 (13.0)	0
Vomiting	3 (13.0)	0
TRAE†	14 (60.9)	2 (8.7)

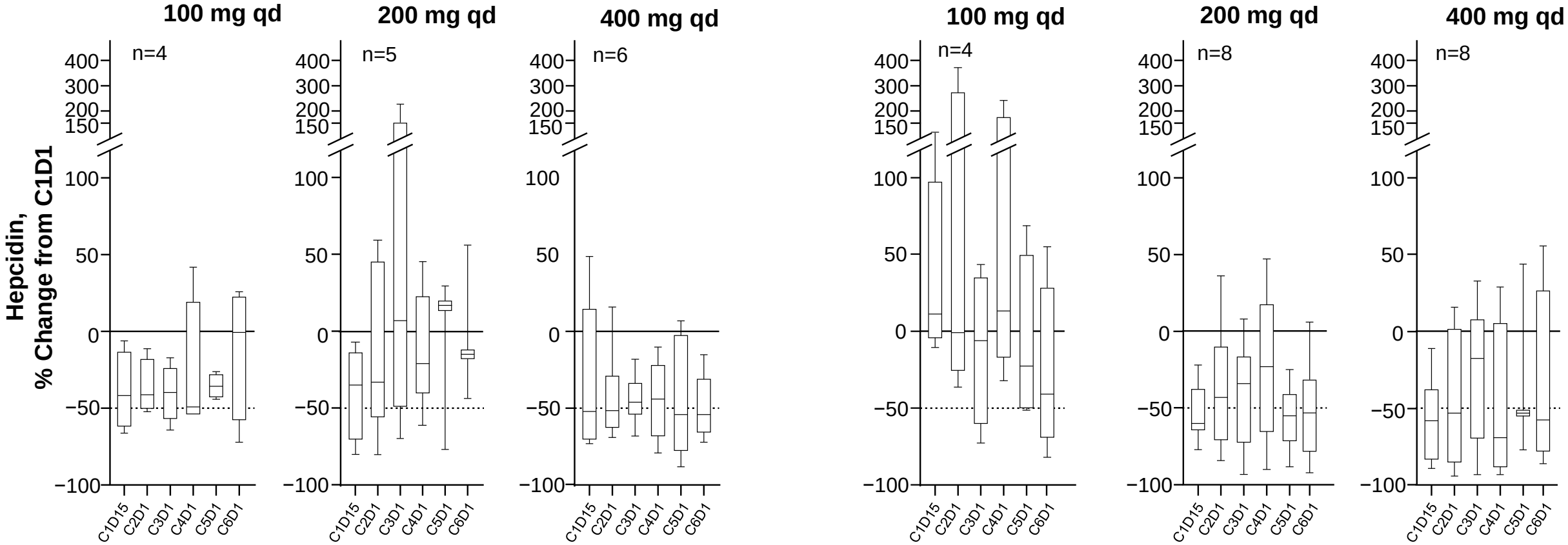
Zilurgisertib Add-on to Ruxolitinib (n=22)		
Event, n (%)	**Any grade**	**Grade ≥3**
Most common TEAE*		
Diarrhea	5 (22.7)	0
Hyperkalemia	5 (22.7)	0
Pain in extremity	4 (18.2)	0
Asthneia	3 (13.6)	1 (4.5)
Dizziness	3 (13.6)	1 (4.5)
Thrombocytopenia	3 (13.6)	1 (4.5)
Alopecia	3 (13.6)	0
Blood creatinine increased	3 (13.6)	0
Decreased appetite	3 (13.6)	0
Dyspnea	3 (13.6)	0
Edema peripheral	3 (13.6)	0
Muscular weakness	3 (13.6)	0
Urinary tract infection	3 (13.6)	0
TRAE†	12 (54.5)	1 (4.5)

MTD= maximum tolerated dose; TEAE= treatment-emergent adverse event; TRAE= treatment-related adverse event.
* Any grade occurring in ≥10% of patients. † Zilurgisertib-related per by study investigator.

Zilurgisertib Hepcidin Suppression Observed in Both Treatment Groups

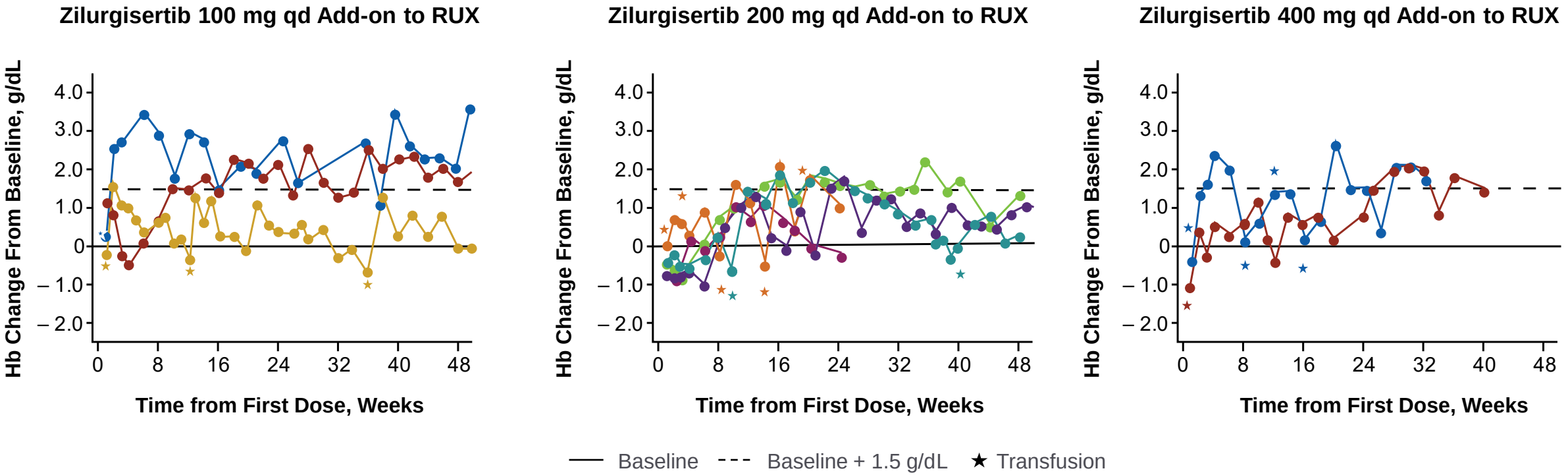
Zilurgisertib Monotherapy

Zilurgisertib Add-on to Ruxolitinib



C= cycle; D= day; qd= once daily.
Data shown for patients who completed ≥1 treatment cycle.

Zilurgisertib Plus Ruxolitinib Maintains and Improves Hemoglobin Levels



NTD= nontransfusion dependent; qd= once daily; TD= transfusion dependent

* Defined as Hgb increase ≥1.5 g/dL relative to baseline; † Hgb improvement for any rolling 12-week period during weeks 1–24.

Zilurgisertib ± Ruxolitinib: Conclusion and Next Steps

- ✓ Reduction in hepcidin levels observed at all dose levels with both monotherapy and in combination with ruxolitinib, with greater control of hepcidin over time observed at higher doses
  - ✓ Maximum hepcidin reduction likely at higher doses
- ✓ Preliminary improvements in anemia observed
- ✓ Zilurgisertib monotherapy or in combination with ruxolitinib was generally well-tolerated
  - ✓ Predominantly grade 1/2 TEAEs
  - ✓ MTD has not been reached

Next Steps

- Dose escalation across all three treatment groups ongoing
- Clinical proof-of-concept anticipated by mid-2024

TEAE= treatment emergent adverse event; MTD= maximum tolerated dose; RDE= recommended dose for expansion

PATRICK MAYES

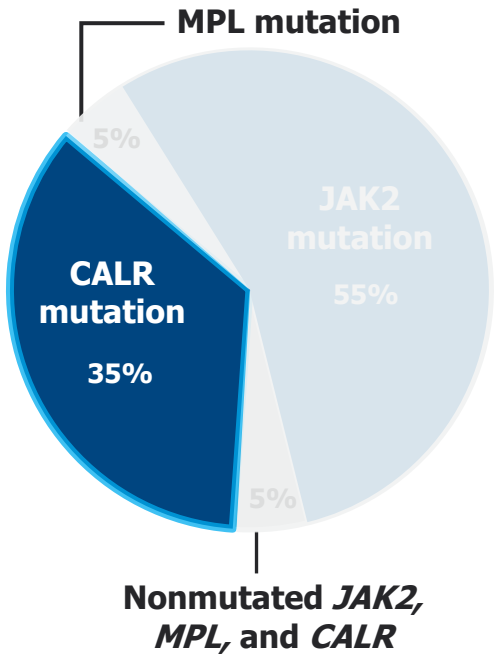
GROUP VICE PRESIDENT & HEAD OF BIOLOGY, INCYTE

Incyte | SOLVE ON.

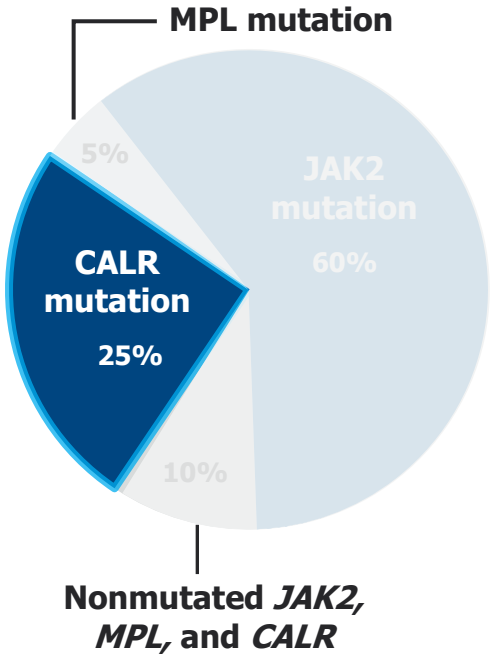
INCA33989: MUTANT CALR ANTAGONIST ANTIBODY

Targeting CALR Mutation to Address Significant Unmet Need in MF and ET

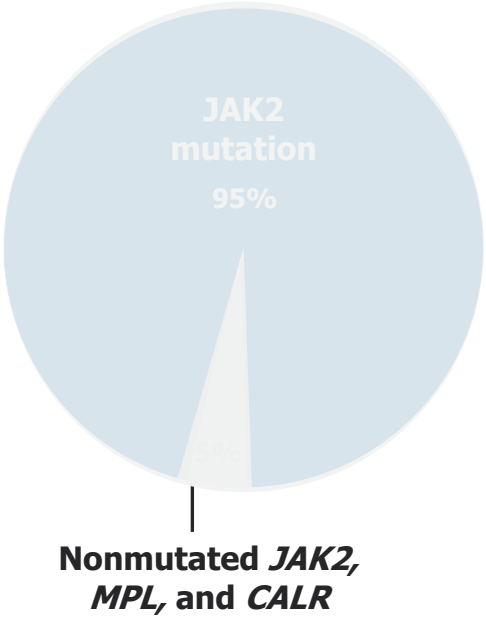
Primary Myelofibrosis



Essential Thrombocythemia



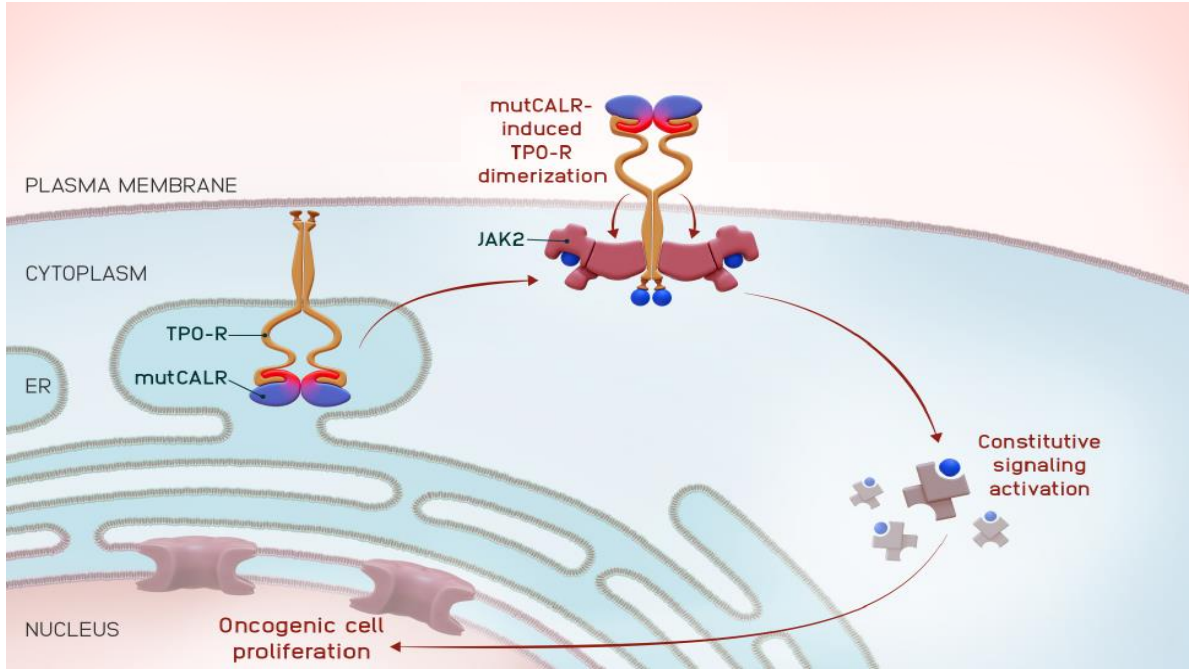
Polycythemia vera



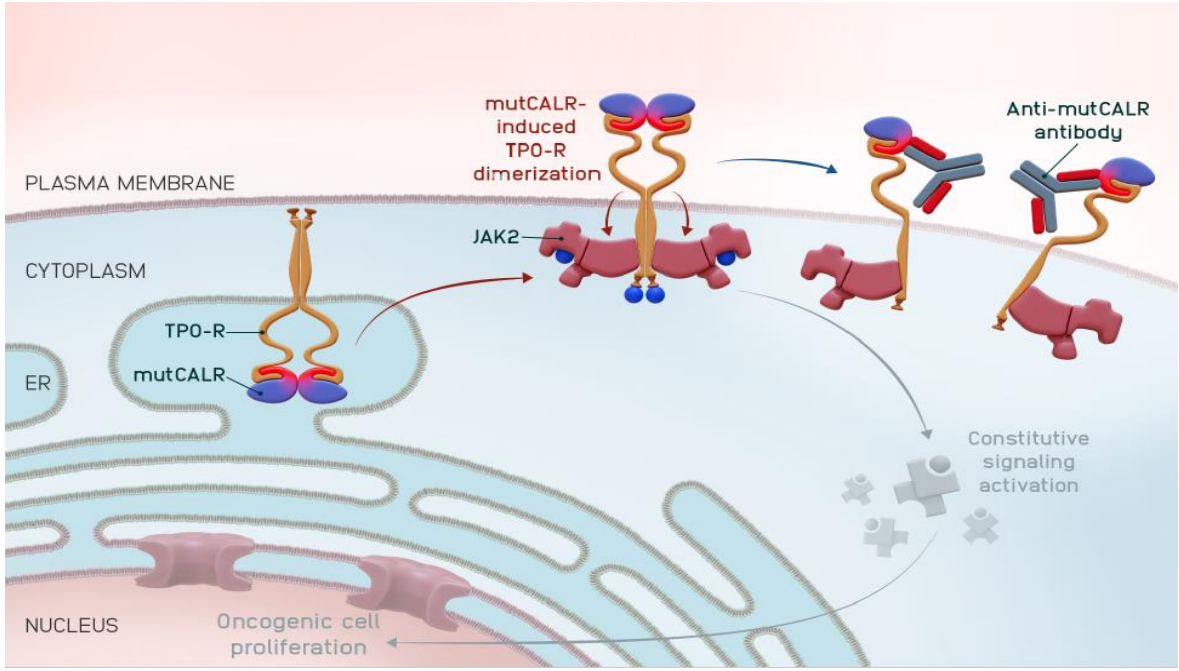
Adapted from Klampfl T, et al. N Engl J Med. 2013;369:2379-2390.

Anti-Mutant Calreticulin (mutCALR) Antibody Mechanism of Action

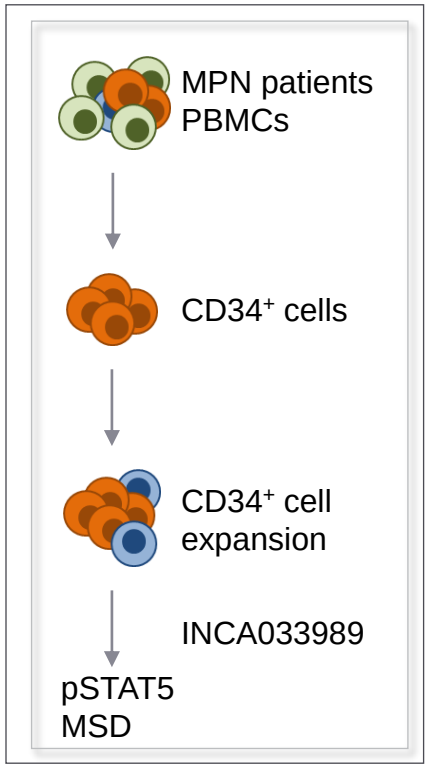
Mutant Calreticulin Induces Oncogenic Cell Proliferation

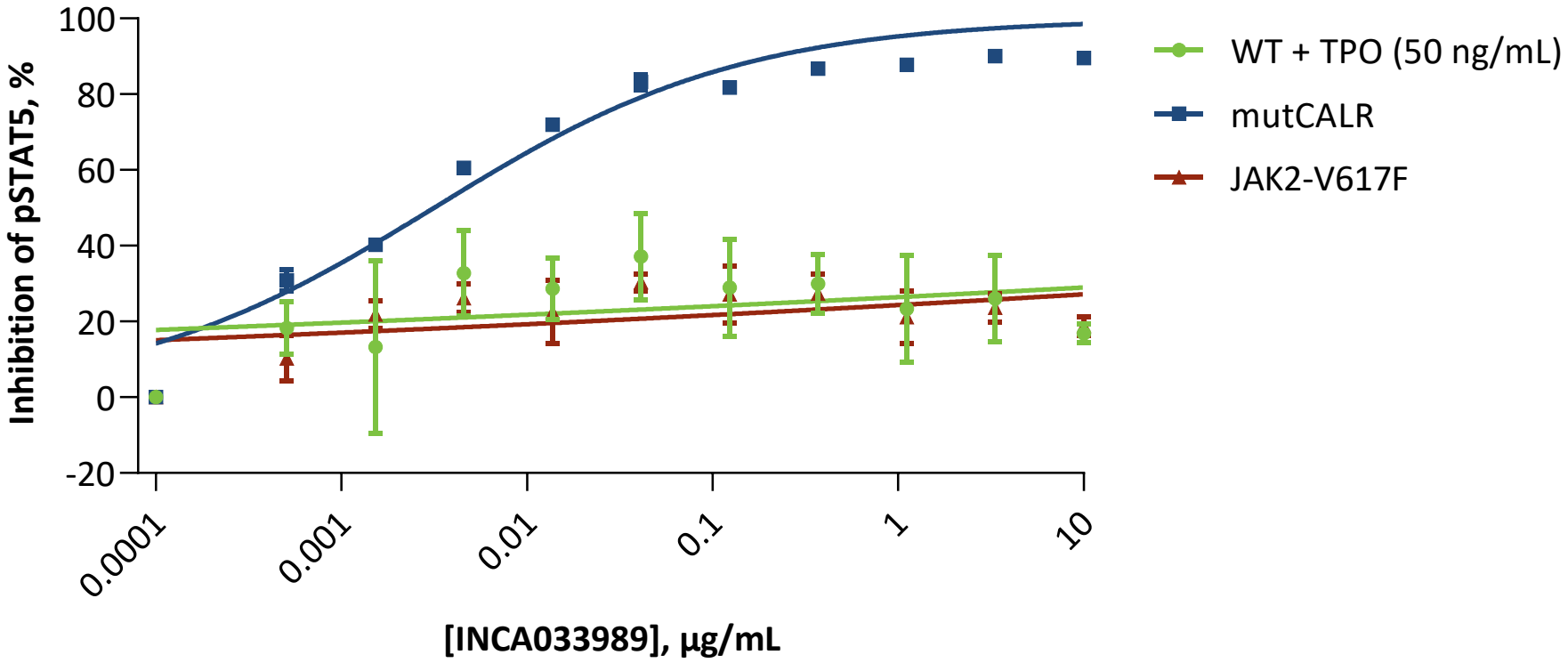


Anti-mutCALR Ab Selectively Inhibits Signaling and Cell Proliferation



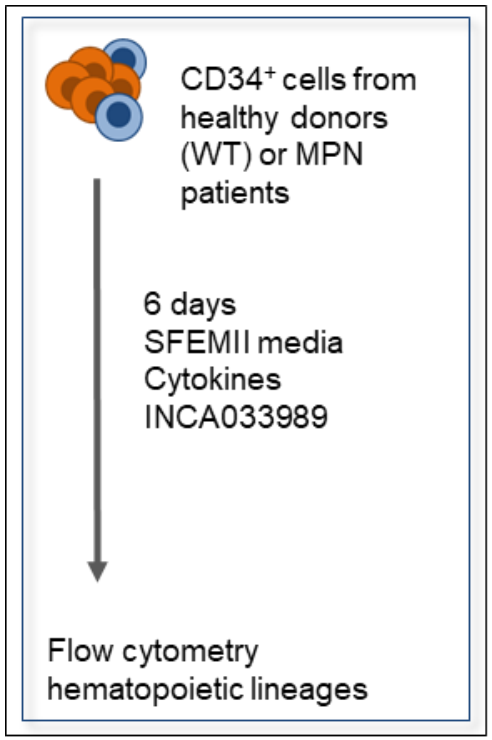
mCALR Ab (INCA033989) Selectively Inhibits pSTAT5 in mutCALR$^+$ Primary CD34$^+$ Cells

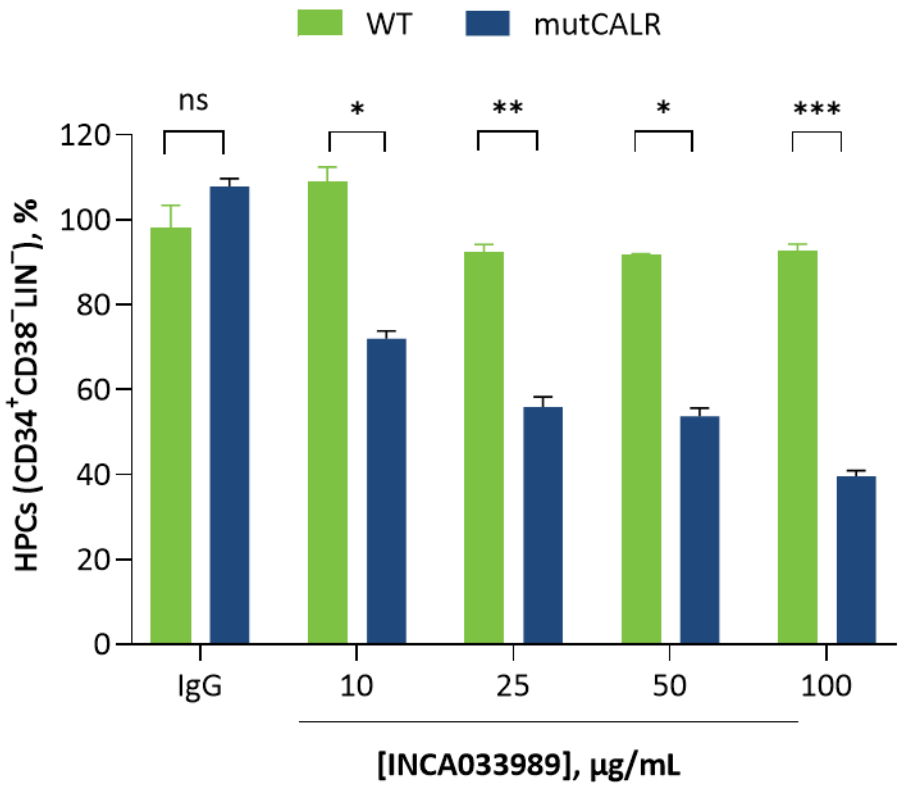


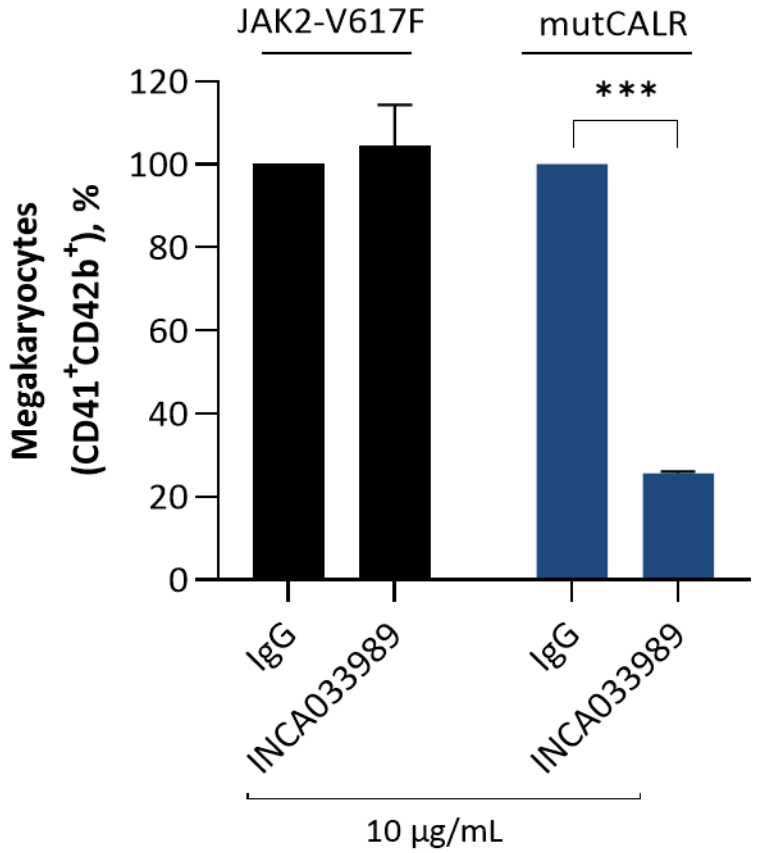


Error bars correspond to SEM and are within the symbol size where not visible.
JAK2= Janus kinase 2; MPN= myeloproliferative neoplasm; PBMC= peripheral blood mononuclear cells; SEM= standard error of the mean.
Incyte data on file

mCALR Ab Selectively Inhibits the Proliferation of mutCALR$^+$ HSPCs from MF Patients





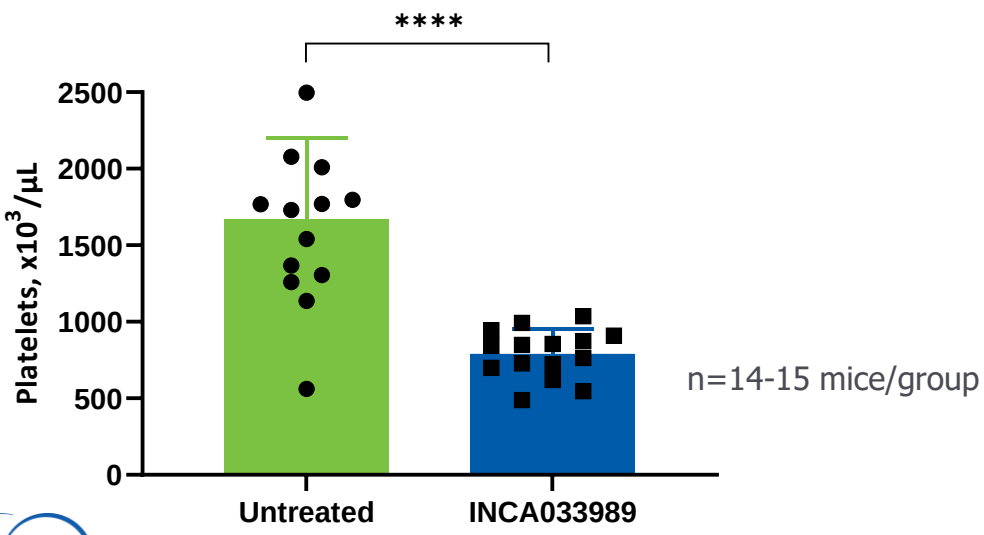


*P<0.01; **P<0.001; ***P<0.0001.
HSPC= hematopoietic stem progenitor cells; ns= not significant
Incyte data on file

mCALR Ab Normalized Platelet Counts and Bone Marrow Environment in a Genetic Model of ET

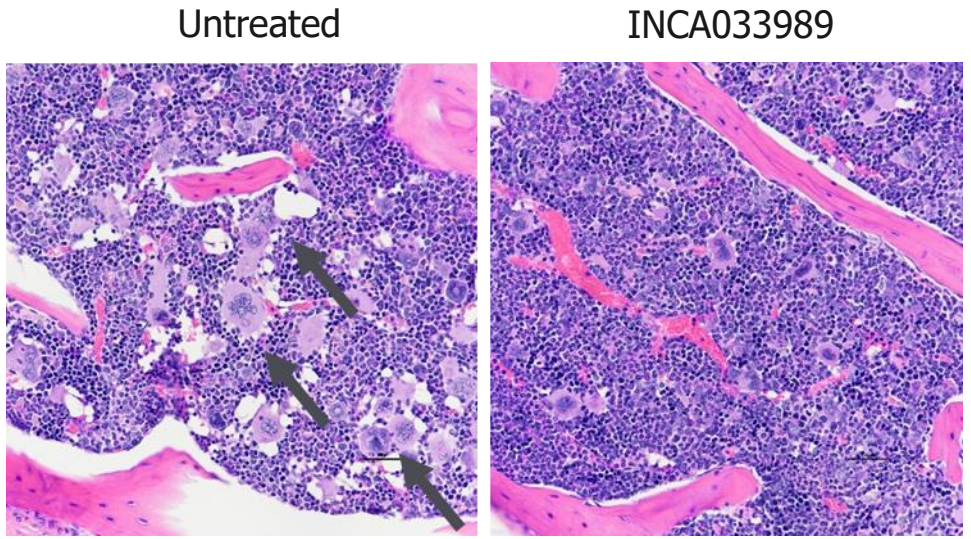
Li et al., Blood. 2018 Feb 8;131(6):649-661.

Platelet counts



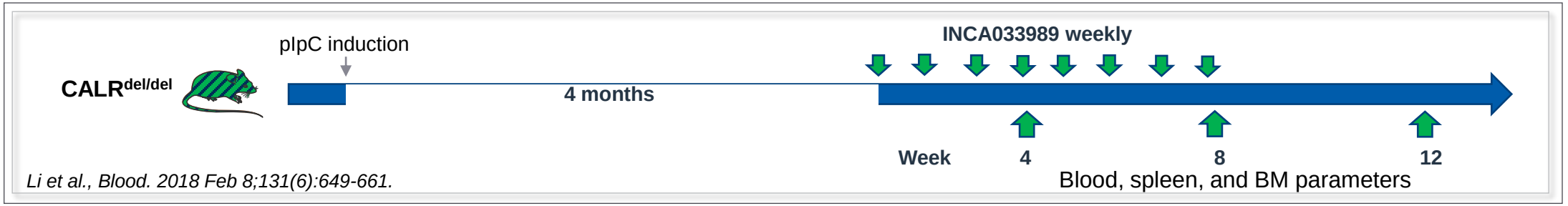
n=14-15 mice/group

Bone marrow environment



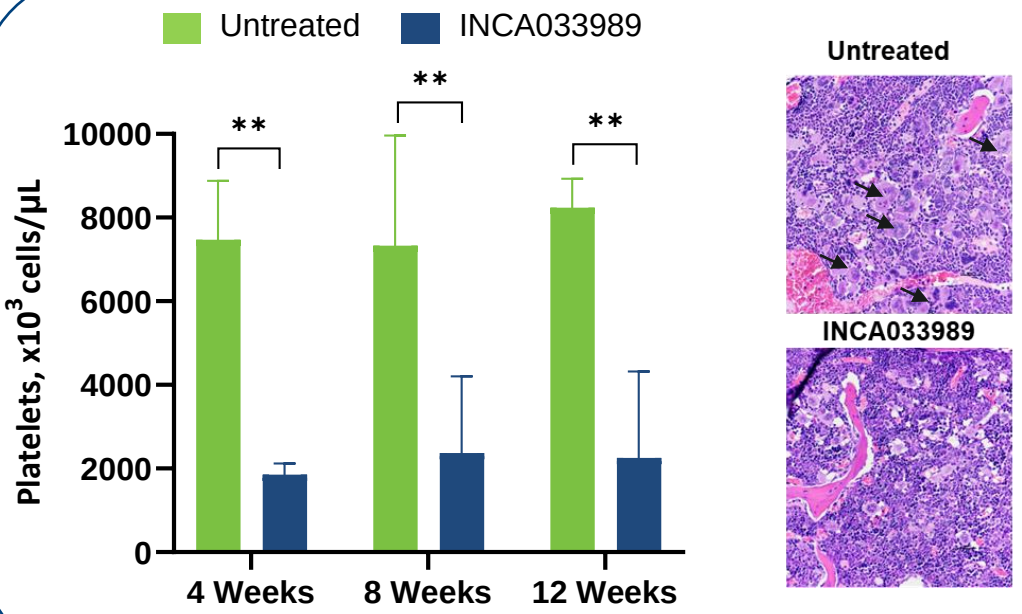
****P<0.0001
pIpC= polyinosinic:polycytidylic acid.
Incyte data on file

mCALR Ab Restores Normal Hematopoiesis and Spleen Size in a Genetic Model of MF



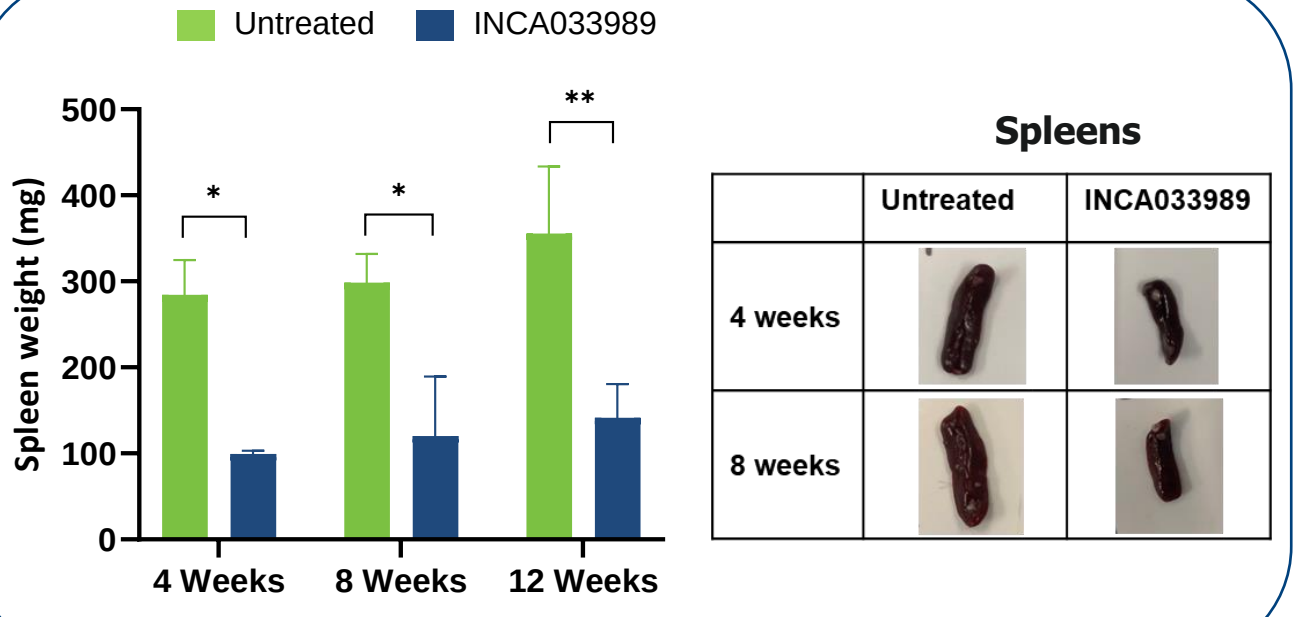
Li et al., Blood. 2018 Feb 8;131(6):649-661.

Normalization of Hematopoiesis



n=5-18 mice/group

Reversal of Splenomegaly



n=2-4 mice/group

*P<0.001; **P<0.0001
pIpC= polyinosinic:polycytidylic acid
Incyte data on file.

INCA033989 Summary

- INCA033989 is a potent antagonist of mutant calreticulin function[1] with potential to be a disease modifying therapeutic
  - Selectively inhibits JAK/STAT signaling and $CD34^+$ cell function in mCALR mutant MF patient samples
  - Normalizes hematopoiesis, platelet count and spleen size in CALR mutant mouse models of ET and MF

- These observations provide rationale for clinical investigation of INCA033989 in MF and ET patients with *CALR* exon 9 mutations[1]

- A Phase 1 study of INCA033989 is ongoing[2] :
  - INCA033989 monotherapy and in combination with ruxolitinib in patients with MF and in monotherapy in ET

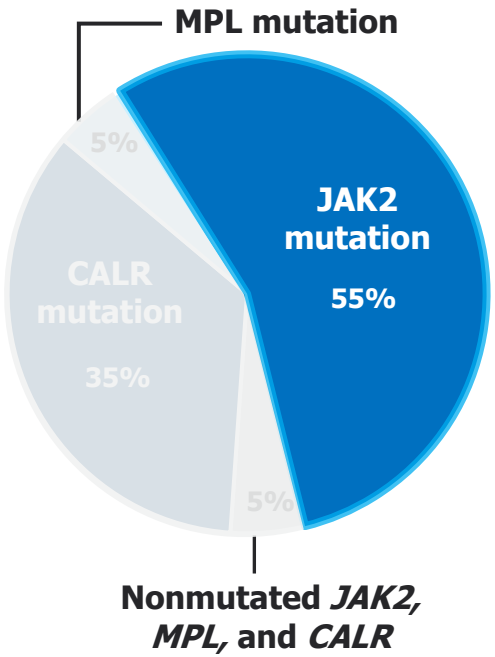
CALR= calreticulin gene; ET= essential thrombocythemia; JAK= Janus kinase; MF= myelofibrosis; mutCALR= mutant calreticulin; STAT= signal transducer and activator of transcription.

1. Reis E, et al. ASH 2022. Oral presentation 6. 2. ClinicalTrials.gov. Accessed Aug 2023. https://www.clinicaltrials.gov/study/NCT05936359.

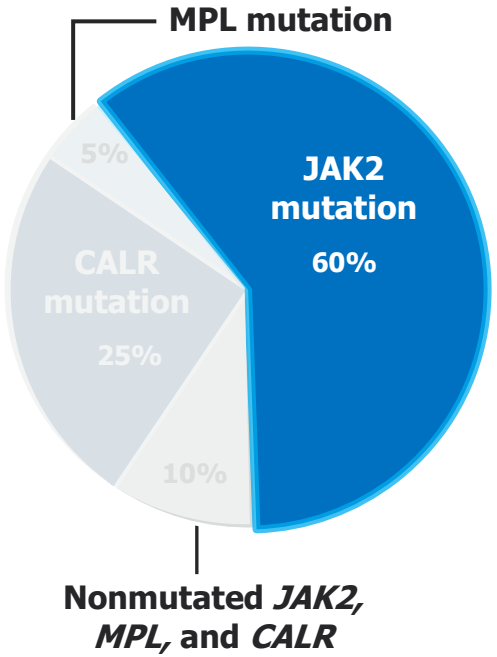
INCB160058: SELECTIVE INHIBITOR OF MUTANT JAK2V617F

Majority of Patients with MPNs could Benefit by Targeting the JAK2 Mutation

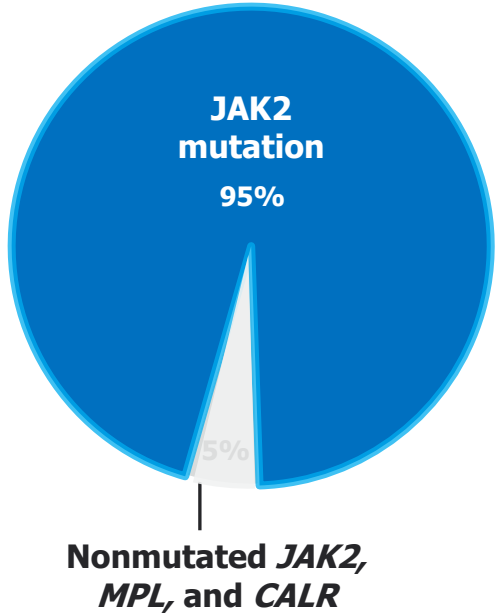
Primary Myelofibrosis



Essential Thrombocythemia



Polycythemia vera

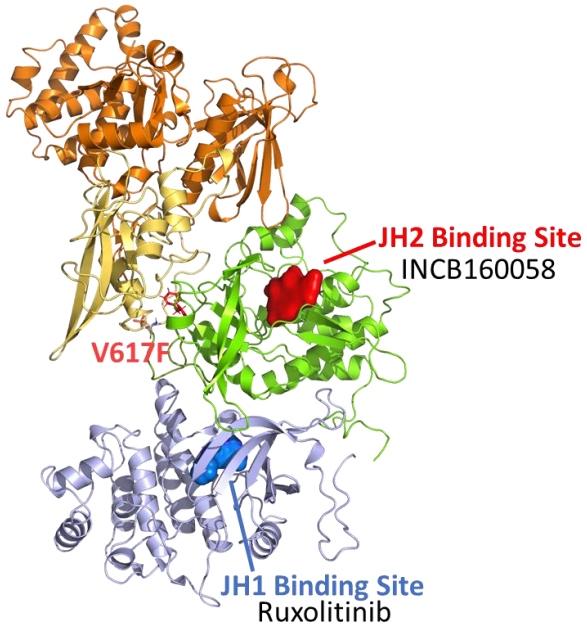


Adapted from Klampfl T, et al. N Engl J Med. 2013;369:2379-2390.

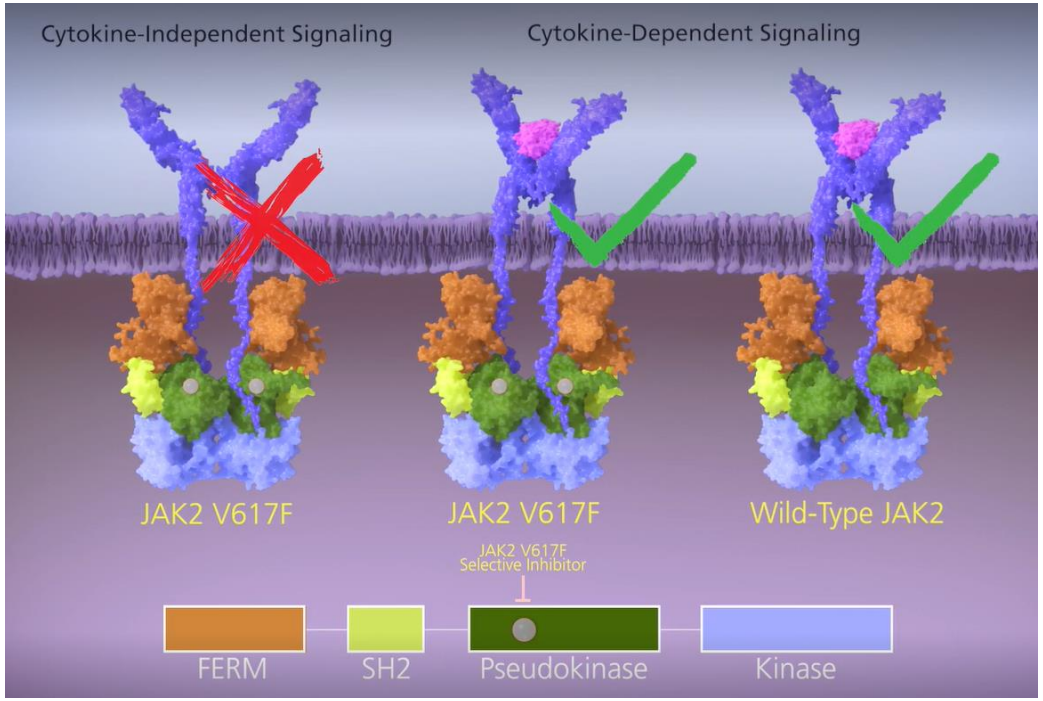
Targeting JAK2 JH2 Site Restores Auto-Inhibition Leading to Selective Inhibition of V617F Signaling

Therapeutic goals of a JAK2V617F-selective inhibitor agent:

- Molecular remission/ disease modification
- Improved hematologic tolerability compared to approved JAK inhibitors



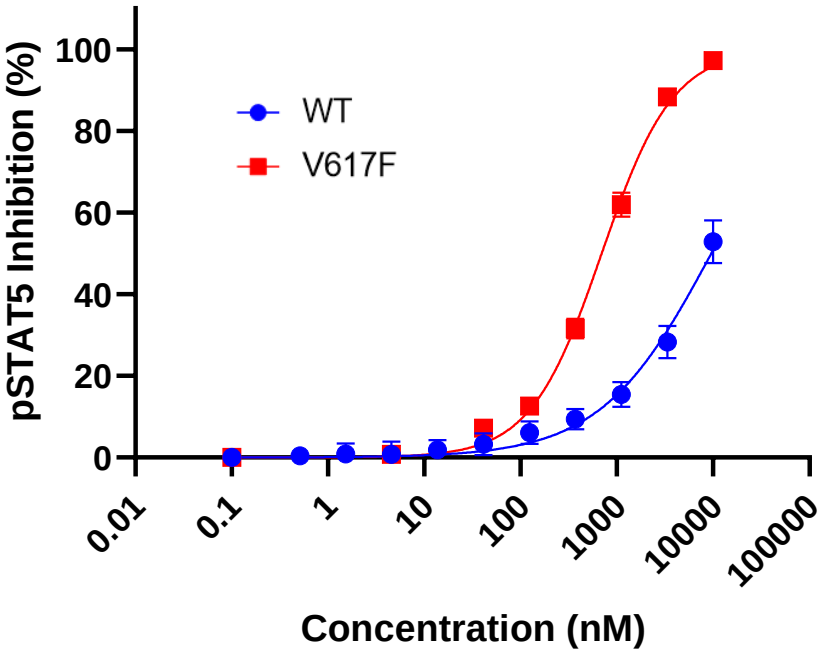
JH2 bound V617F JAK2 kinase is not constitutively active but responds to cytokine stimulation



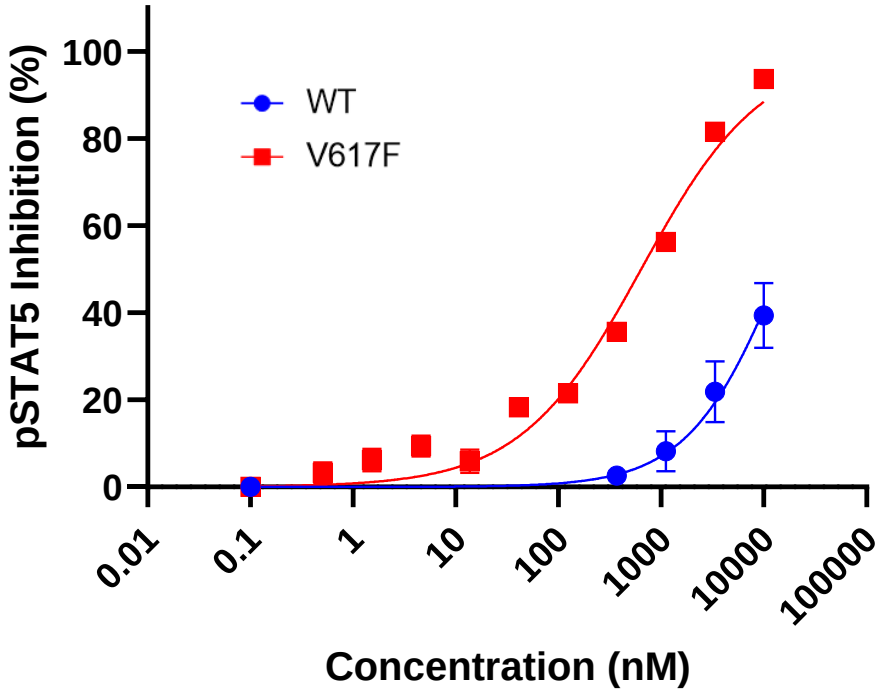
Incyte JH2 binders block constitutively active signaling, while allowing cytokine stimulation, a key feature for selectivity

INCB160058 Selectively Inhibits JAK2V617F Signaling

BaF3 Isogenic Cell Lines



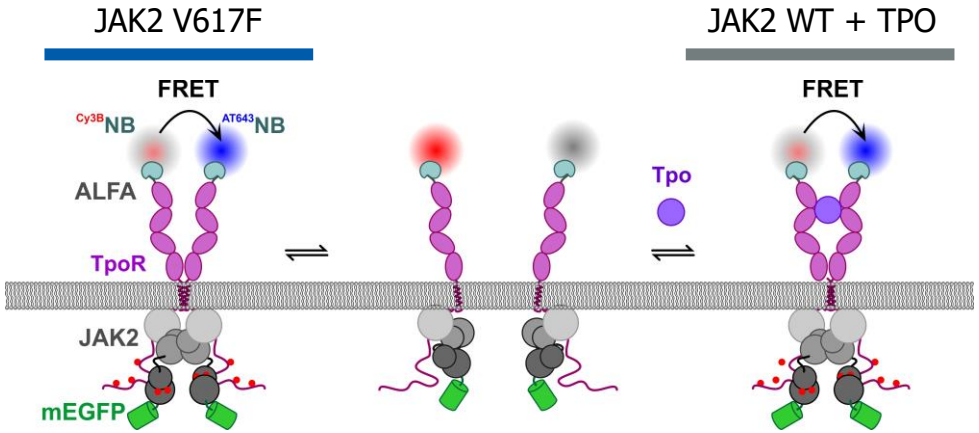
MPN Patient Samples



Avg of 4 independent patient samples

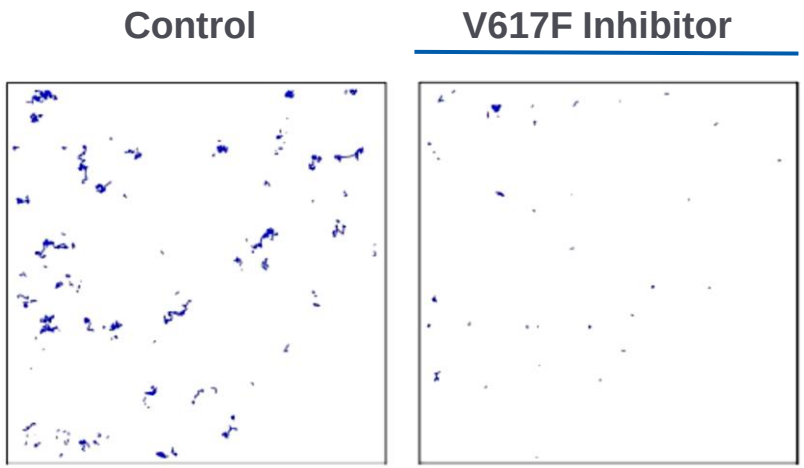
Compounds that Bind Pseudokinase Domain Inhibit JAK2V617F-Induced TPO Receptor Dimerization

Quantification by Single Molecule FRET in Live Cells



Wilmes S, et al. *Science*. 2020;367:643-52.

TPOR Dimerization - Fluorescence



- Receptor dimerization is required for JAK2V617F function
- JH2 binding compounds prevent ligand-independent receptor dimerization through inhibition of mutant JAK2V617F

ALFA= ALFA-tag; DMSO= dimethyl sulfoxide; JAK= Janus kinase; mEGFP= monomeric enhanced green fluorescent protein; NB= anti-ALFA nanobody; TPO= thrombopoietin; TpoR= thrombopoietin receptor; WT= wild-type.

INCB160058 Selectively Inhibits BaF3 Cells Harboring JAK2V617F Mutation

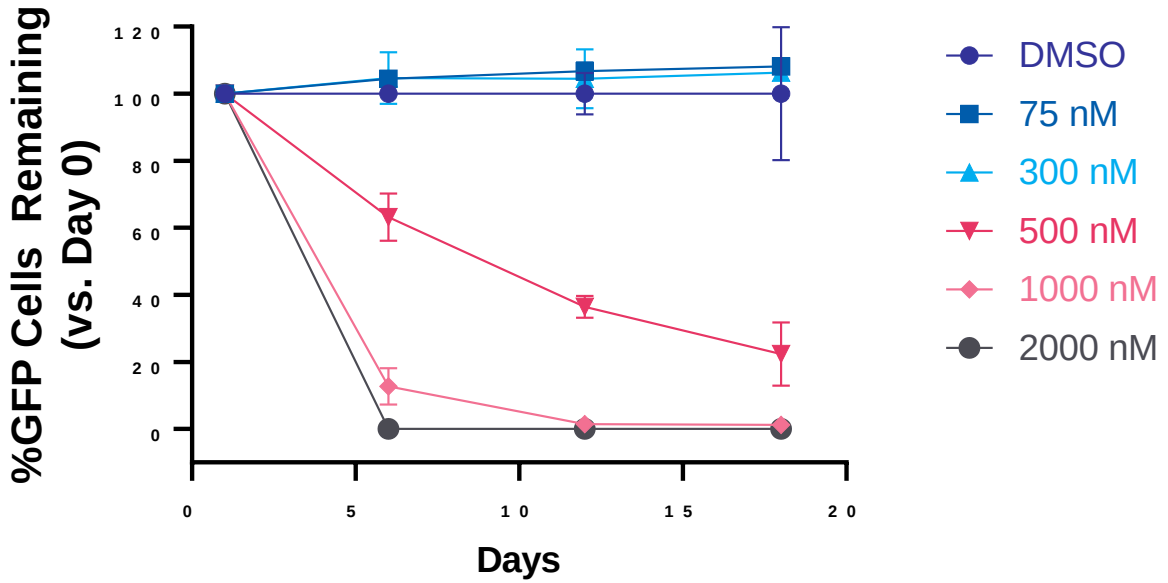
BaF3 Co-culture Assay

JAK2V617F-GFP
+
WT JAK2 (mutant CALR)-untagged

Wash and re-plate with fresh compound every 3 days

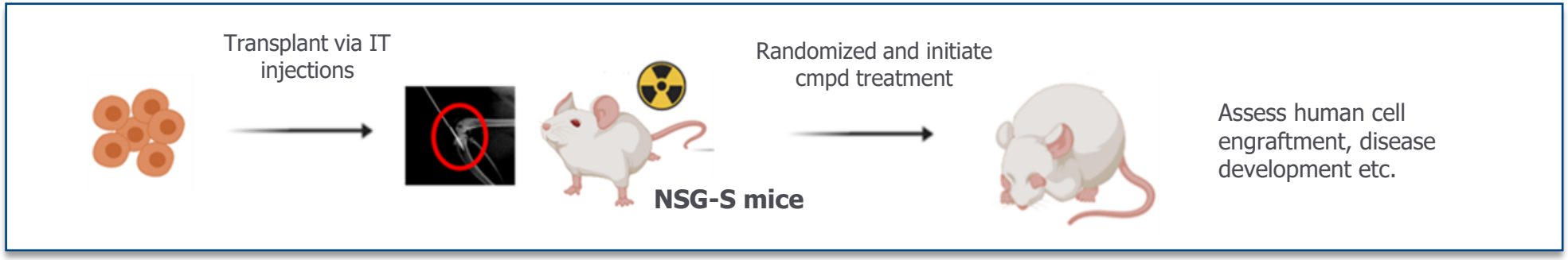
D6 D9 D12 D15 D18

Cell Count

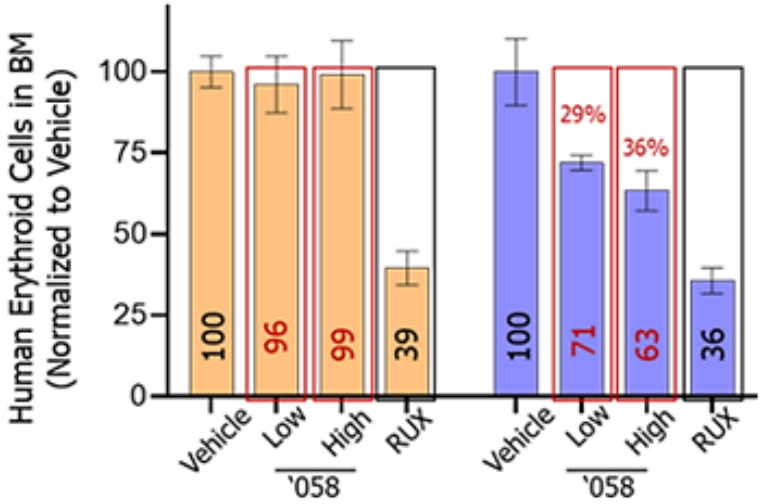


DMSO= dimethyl sulfoxide

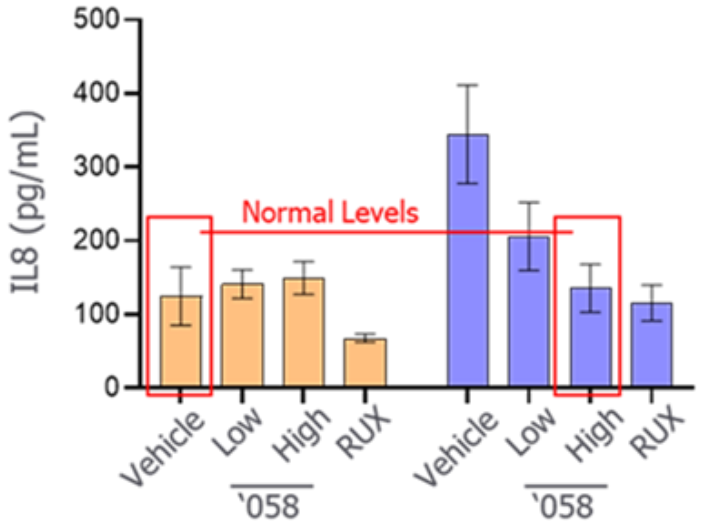
INCB160058 Selectively Inhibits JAK2V617F Cells in a Human MF PDX Model



Selective Inhibition of V617F Mutant Cell Engraftment in the BM



Normalization of Cytokines



Incyte data on file

INCB160058 Summary

- INCB160058 is a potent and selective JAK2 pseudokinase domain binder with potential to be a disease modifying therapeutic
- Pseudokinase binding offers a new mechanism of action for selective inhibition of JAK2V617F, with potential to eradicate mutant clones
- INCB160058 inhibits cytokine independent activity of JAK2V617F while sparing WT JAK2
- Initiation of clinical trials of INCB160058 is expected in Q1 2024

DMSO, dimethyl sulfoxide; JAK, Janus kinase; MPN, myeloproliferative neoplasm; pSTAT, phosphorylated signal transducer and activator of transcription; WT, wild-type.

PETER LANGMUIR

GROUP VICE PRESIDENT

ONCOLOGY TARGETED THERAPEUTICS, INCYTE

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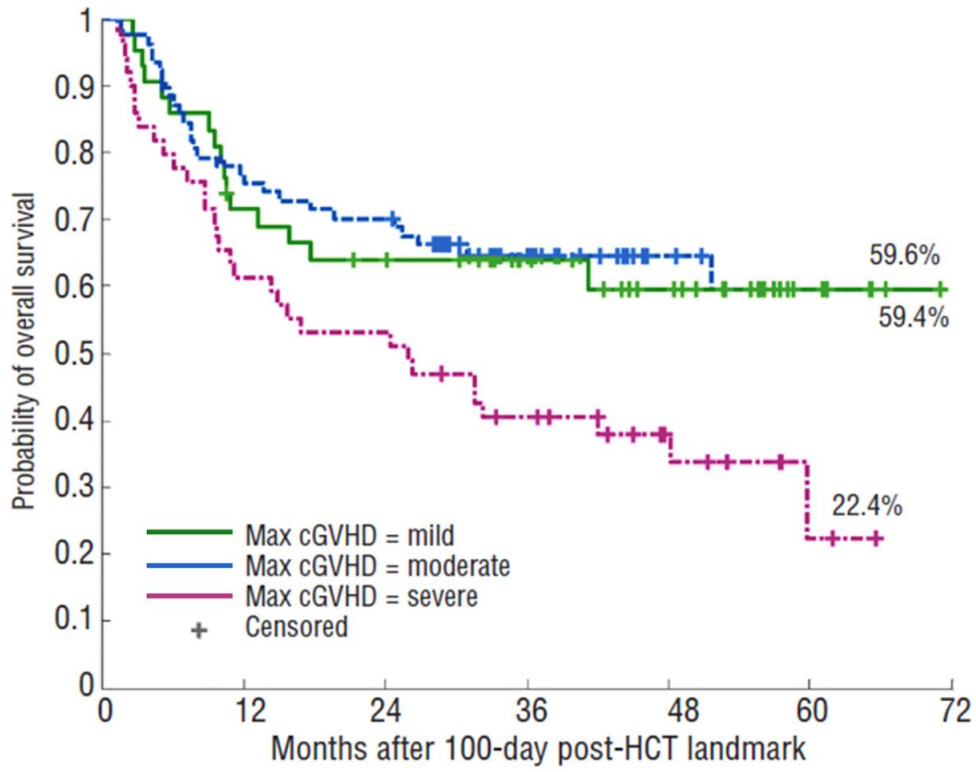
AXATILIMAB (ANTI-CSF-1R)

cGVHD is a Major Cause of Late Morbidity and Mortality in Allo-HSCT Recipients

- Chronic graft-versus-host disease is a major cause of late morbidity and the leading cause of NRM in patients surviving >2 years after allo-HSCT[1]
- Reported 2-year OS for cGVHD patients are 60–80%

Overall survival[2,a]

n=168[b] (overlap and classic cGVHD)



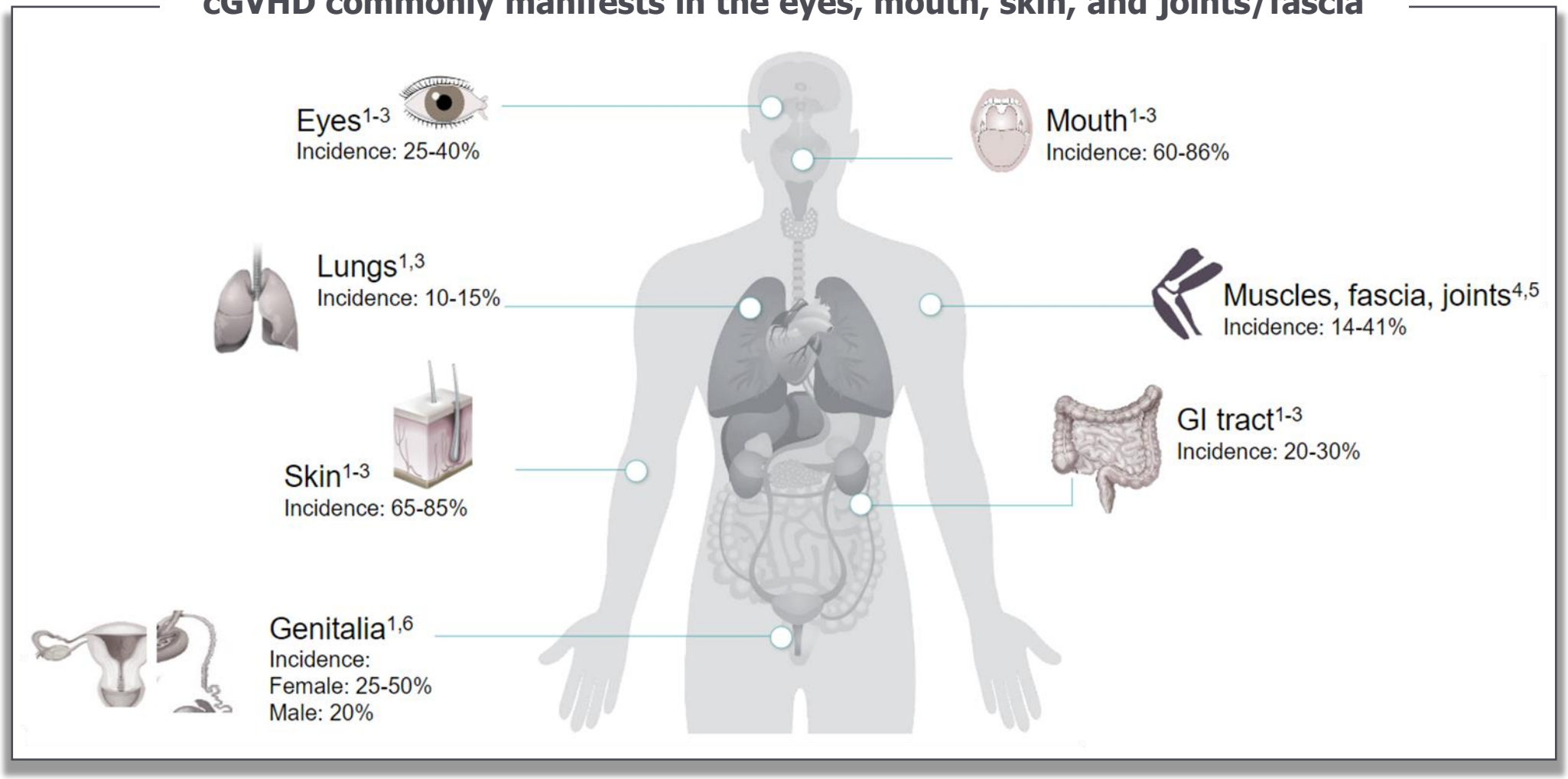
NRM= nonrelapse mortality; HSCT= hematopoietic stem cell transplantation

1. Lee SJ. Best Pract Res Clin Haematol. 2010;23:529–35. 2. Pidala J, et al. *Haematologica*. 2011;96:1678–84.

[A] Overall survival according to NIH global severity and type of cGVHD onset

cGVHD is an Inflammatory and Fibrotic Multi-Organ Disease

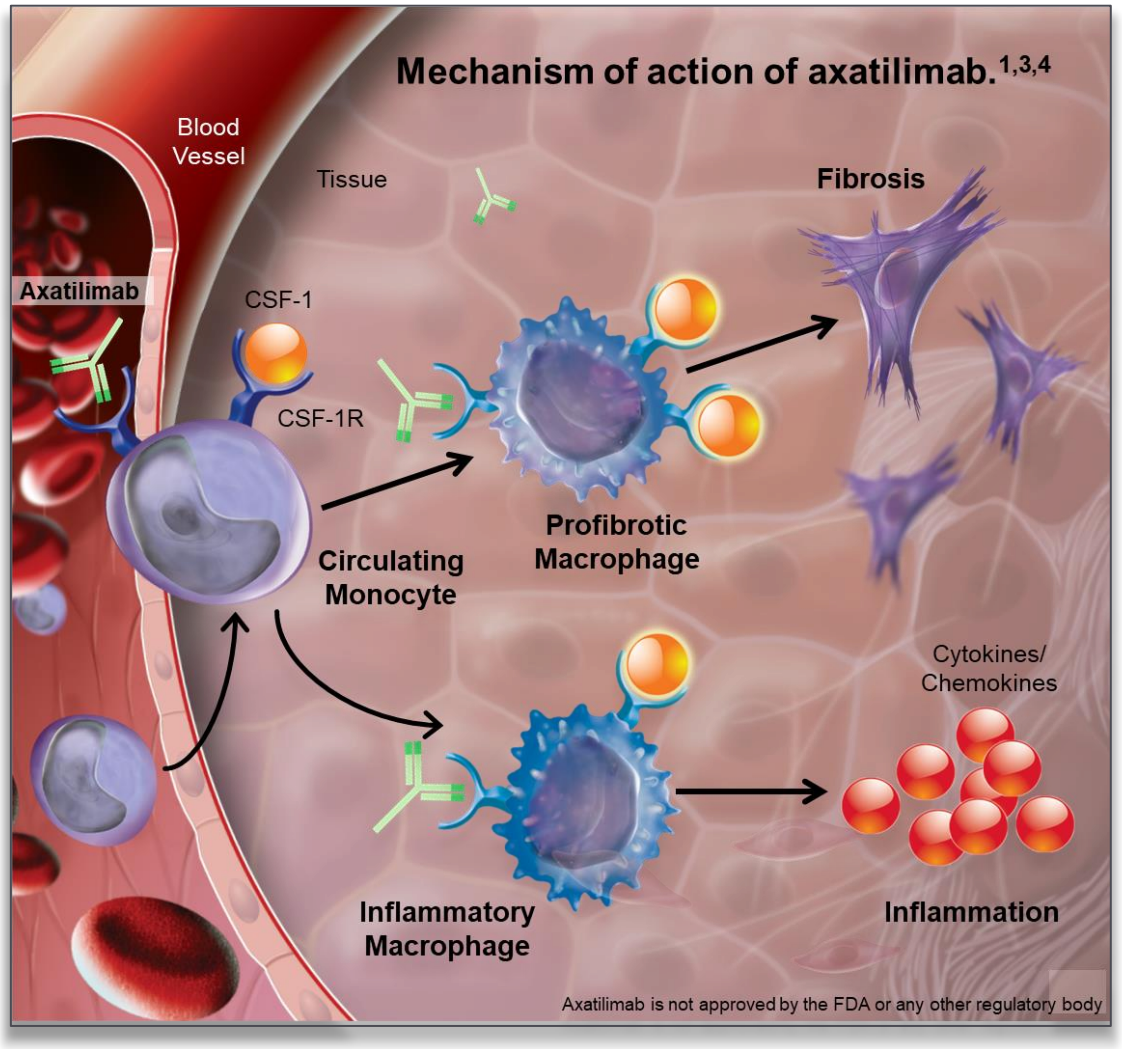
cGVHD commonly manifests in the eyes, mouth, skin, and joints/fascia



1. JagasiaMH, et al. BiolBlood MarrowTransplant. 2015;21(3):389-401. 2. VigoritoAC, et al. Blood. 2009;114(3):702-708. 3. Lee SJ, et al. Blood. 2002;100(2):406-414. 4. VukicT, et al. Croat Med J. 2016;57(3):266-275.5. InamotoY, et al. Arthritis Rheumatol. 2014;66(4):1044-1052. 6. Hamilton BK, et al. Bone Marrow Transplant. 2017;52(6):803-810.

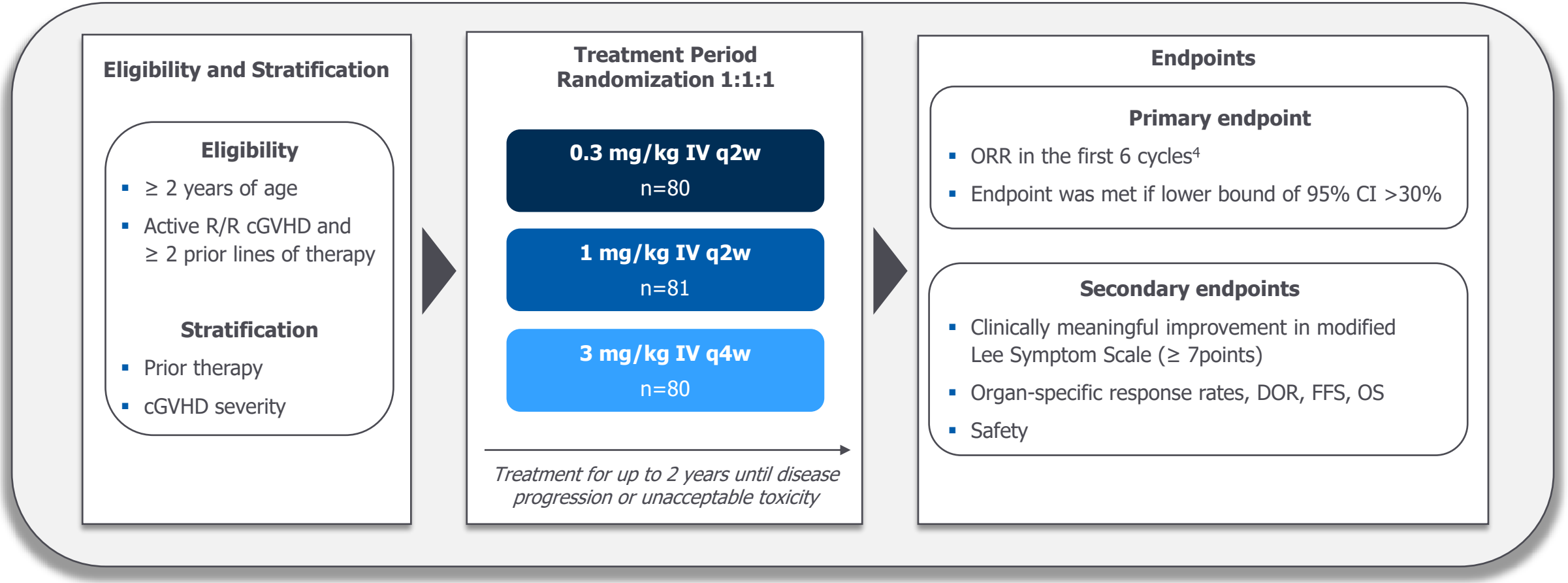
Axatilimab Targets Key Mediators of cGVHD Pathology

- CSF-1R–dependent monocytes and macrophages are key mediators in inflammation and fibrosis in cGVHD[1,2]
- Axatilimab is a monoclonal antibody that targets CSF-1R[2]
- Phase 1/2 study of axatilimab in patients with advanced, recurrent/refractory cGVHD showed favorable safety and promising efficacy[2]
  - Aggregate ORR in the first 6 cycles of 67%



1. MacDonald et al. Blood. 2017;129:13-21. 2. Kitko et al. J Clin Oncol. 2022;41:1864-1875. 3. Jagasia et al. Biol Blood Marrow Transplant. 2015;21:389-401. 4. Jardine et al. J Clin Invest. 2020;130:4574-4586.

AGAVE-201: Global Phase 2 Study Evaluating Safety and Efficacy of Axatilimab in Patients with cGVHD



cGVHD= chronic graft-versus-host disease

1. MacDonald et al. Blood. 2017;129:13-21. 2. Kitko et al. J Clin Oncol. 2022;41:1864-1875. 3. Jagasia et al. Biol Blood Marrow Transplant. 2015;21:389-401. 4. Jardine et al. J Clin Invest. 2020;130:4574-4586. 4. As defined by NIH 2014 Consensus Criteria

AGAVE-201: Baseline Characteristics (ITT Population)

Patient characteristic	Total cohort (N=241)
Age, median (min, max), y	53 (7, 81)
Sex, male, n (%)	151 (62.7)
Race, White, n (%)	200 (83.0)
Time from cGVHD diagnosis to randomization, median (min, max), y	**4.01 (0.4, 17.6)**
Number of prior systemic cGVHD therapy, median (min, max)	**4 (2, 15)**
Prior systemic cGVHD therapy[a], n (%)	**204 (84.6)**
Prior ibrutinib, n (%)	**75 (31.1)**
Prior ruxolitinib, n (%)	**179 (74.3)**
Prior belumosudil, n (%)	**56 (23.2)**
Number of organs involved at baseline, median (min, max)	4 (0, 8)[b]
≥ 4 organs involved, n (%)	130 (53.9)
Patients with severe disease, n (%)	192 (79.7)

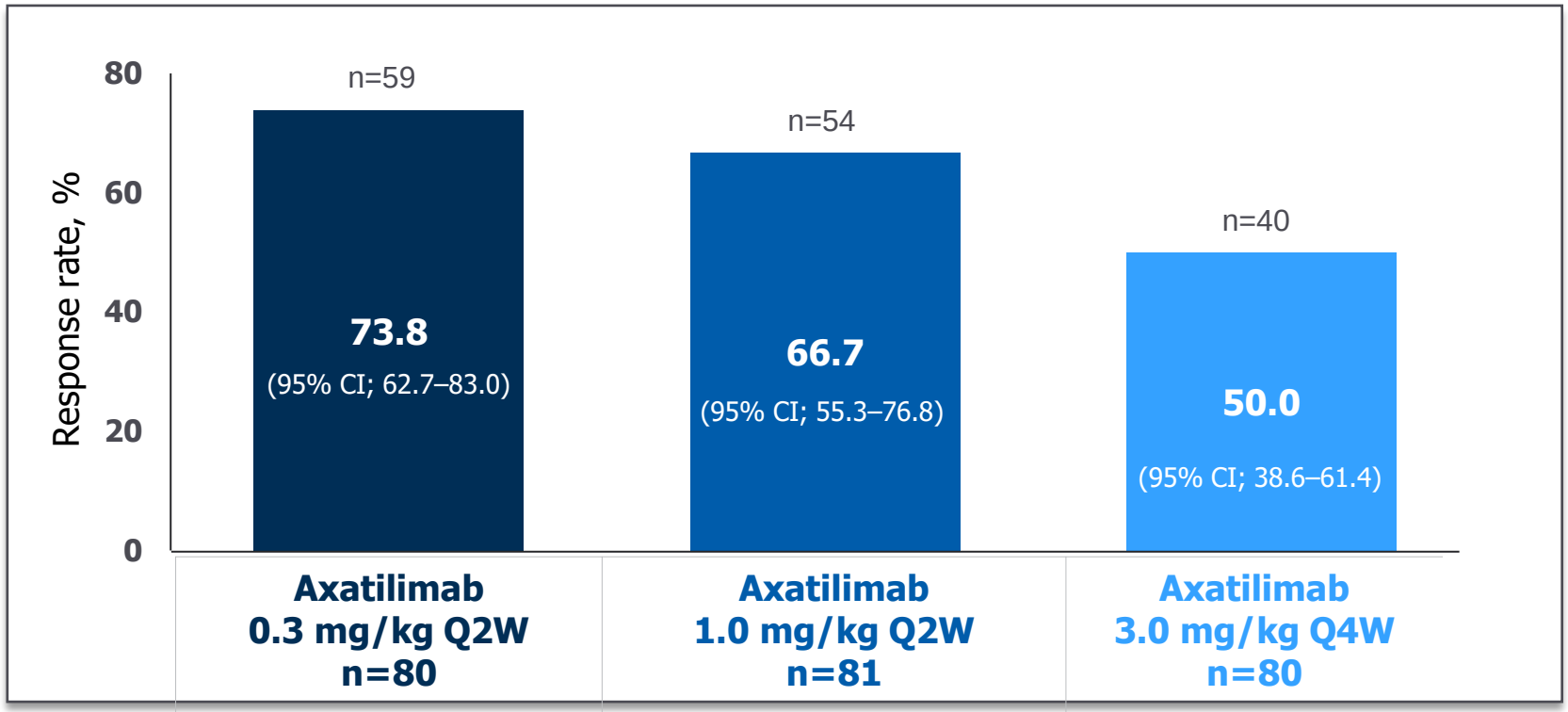
cGVHD= chronic graft-versus-host disease; ITT= intention to treat; max= maximum; min= minimum

a) Prior use of at least 1 of the following therapies: ibrutinib, ruxolitinib, or belumosudil. b) No patients on study had 0 organs involved. 2 patients consented but withdrew from study before the first dosing visit, in which organ involvement information was collected.

AGAVE-201: Primary Efficacy Endpoint Met in All Cohorts

Primary endpoint

ORR in the first 6 cycles as defined by NIH 2014 Consensus Criteria[2] **was met in all 3 dose cohorts**

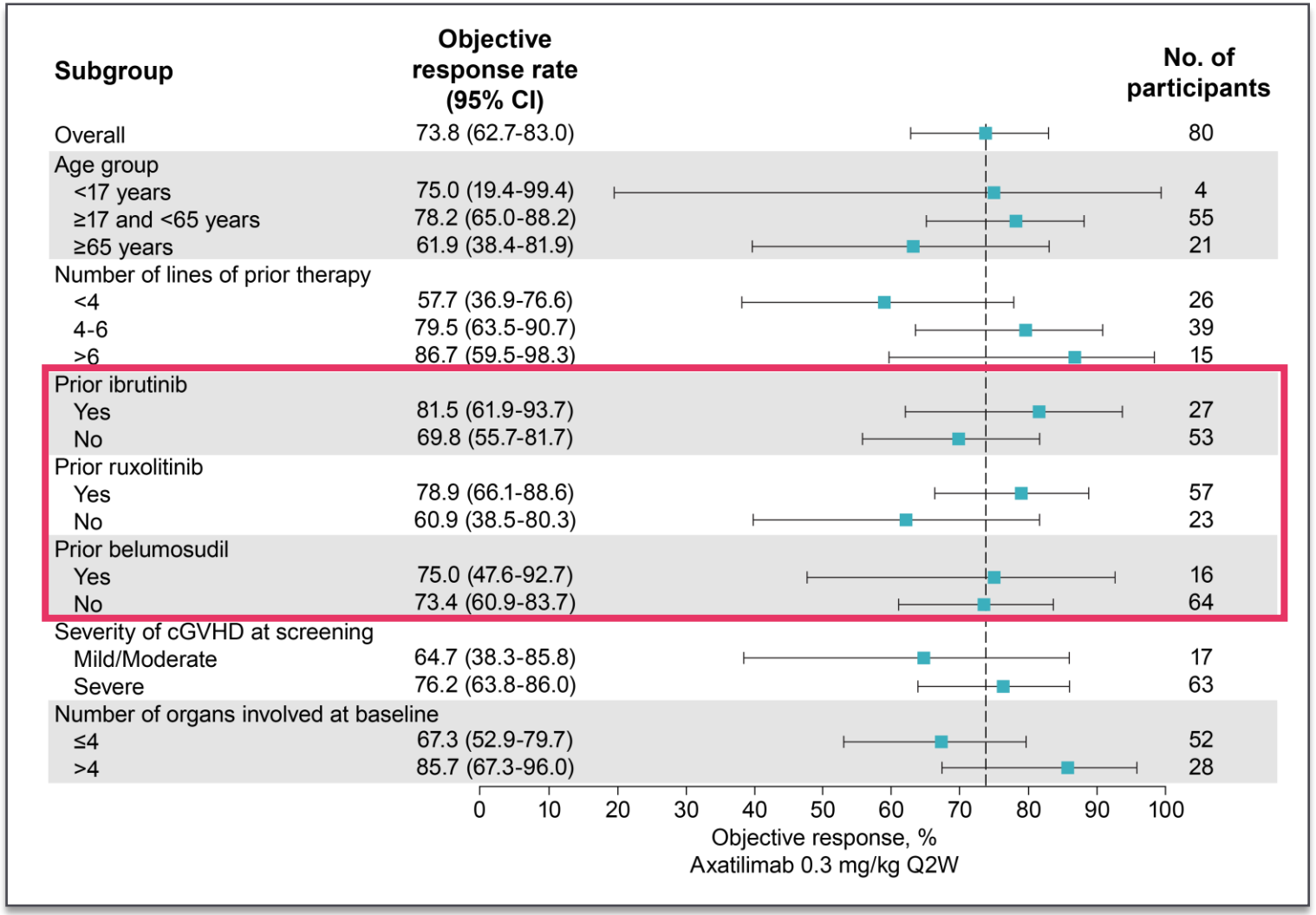


Time to response, median months (range)	1.7 (0.9–8.1)	1.9 (0.9–8.6)	1.4 (0.9–5.6)
Durable response at 12 months, % (95% CI)	60 (43–74)	60 (43–74)	53 (30–71)

ORR= objective response rate

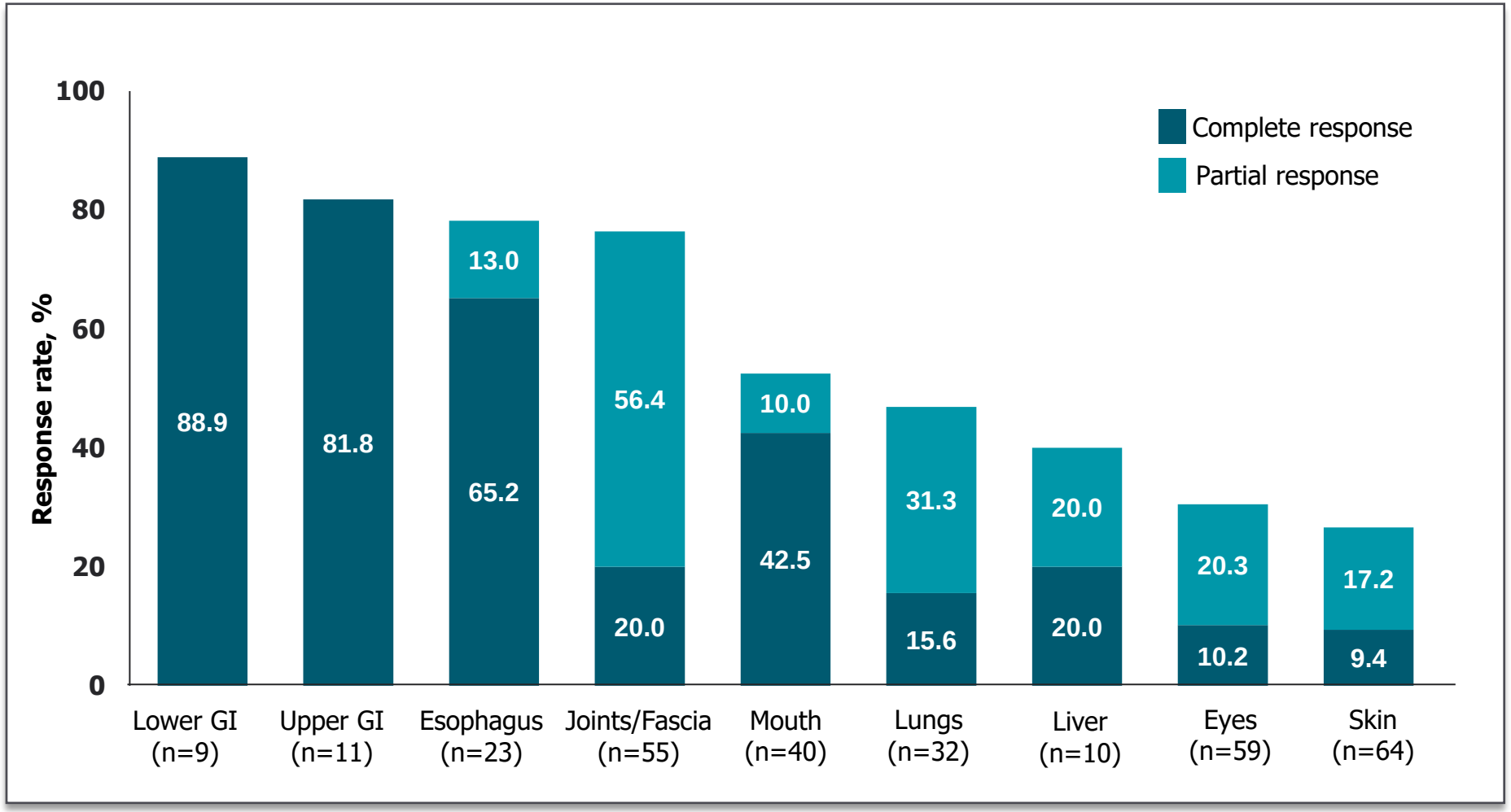
AGAVE-201: Efficacy Across Subgroups in 0.3 mg/kg Q2W

High response rates (≥75%) were seen in patients who received prior FDA-approved therapies



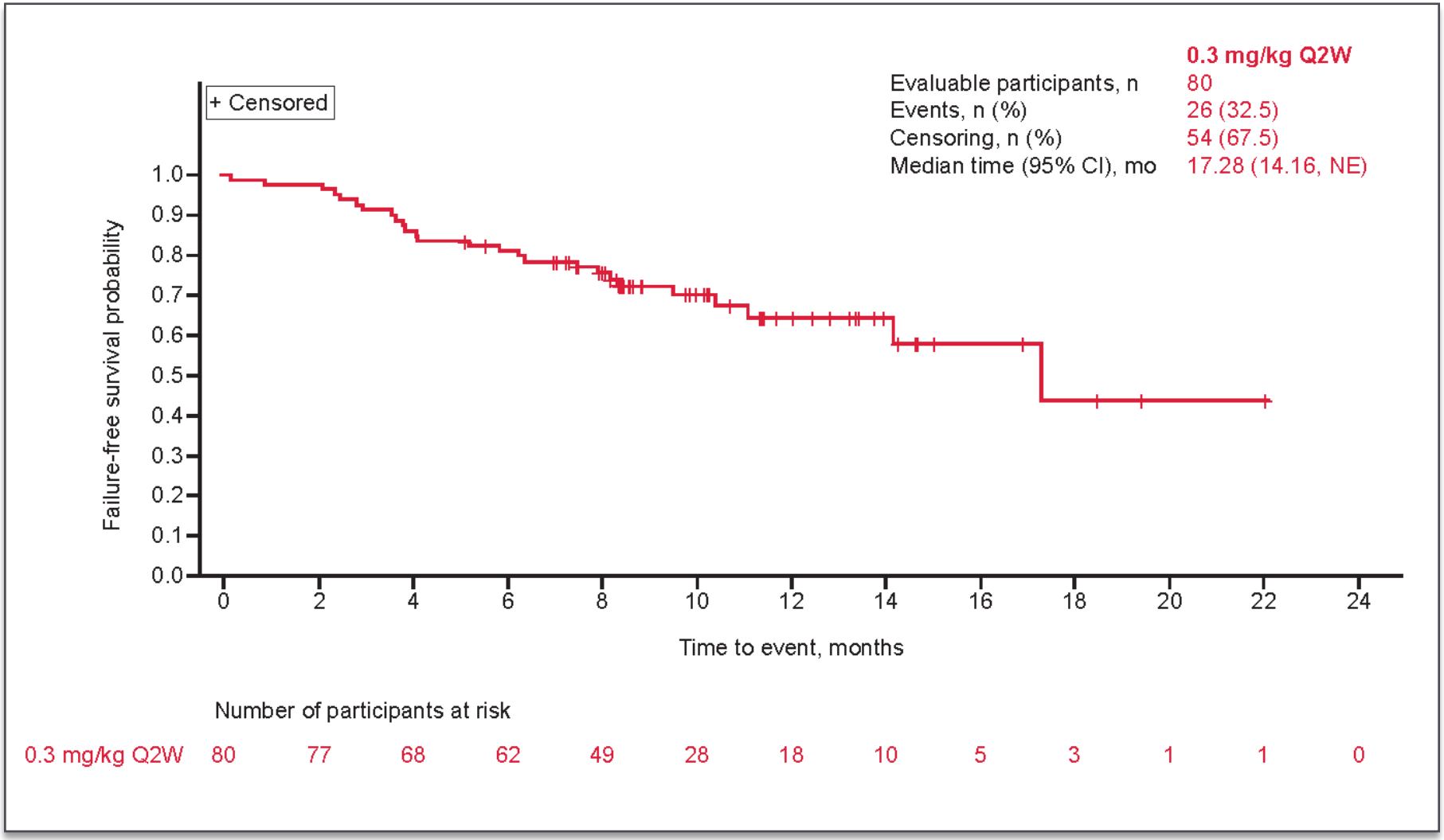
AGAVE-201: Organ-specific Responses in 0.3 mg/kg Q2W

Responses observed across multiple organs



AGAVE-201: Failure-Free Survival

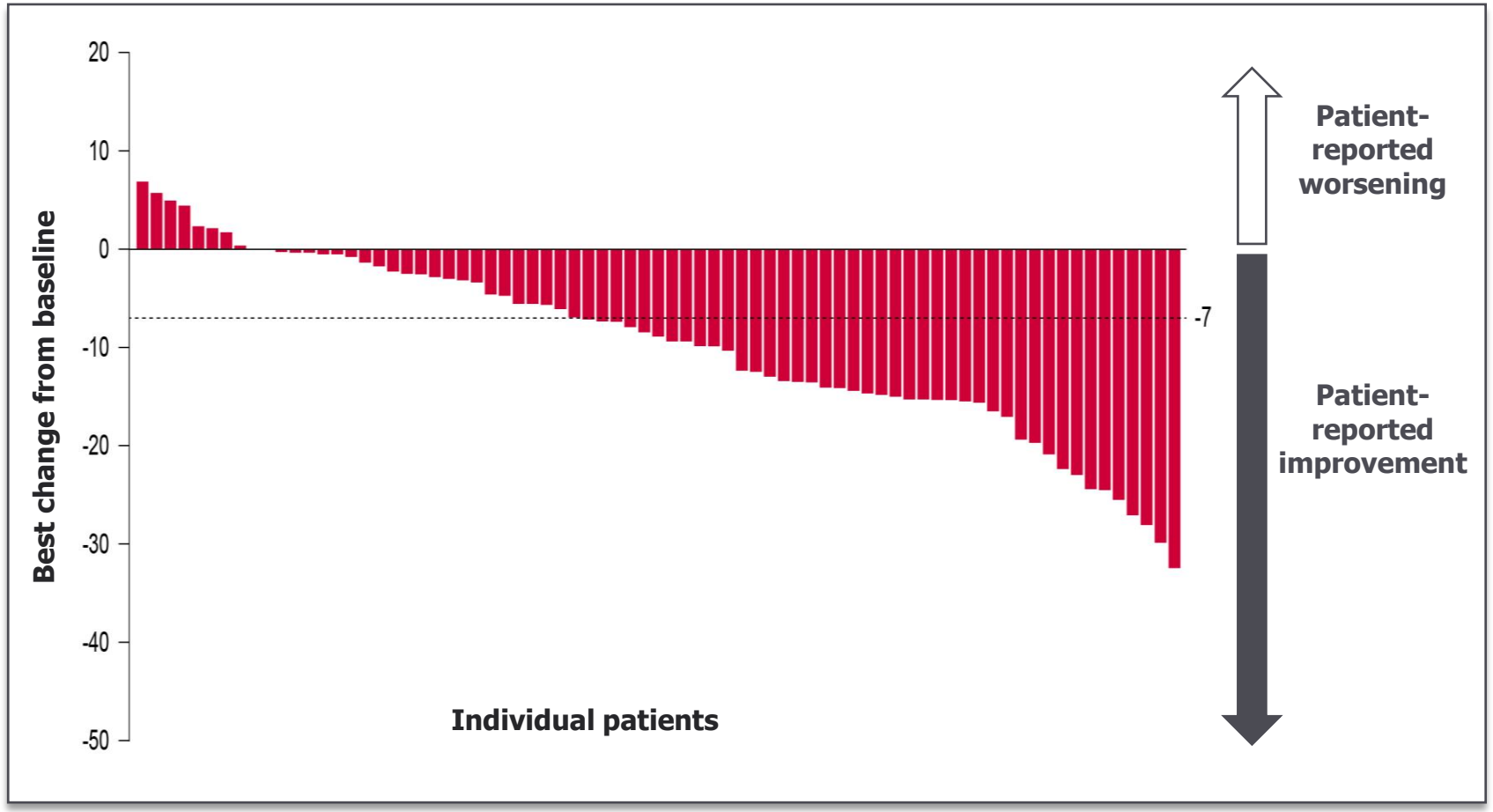
Median (range) FFS: 17.3 (14.2–NE) months



Failure-free survival (FFS): Events are initiation of a new systemic chronic GVHD treatment, recurrent malignancy, and death

AGAVE-201: Symptom Improvement at 0.3 mg/kg Q2W

- **~87% had mLSS score improvement from baseline**
- **55% clinically meaningful change of ≥7-point improvement in mLSS score**
- **Median time to ≥7-point mLSS improvement was 1.5 months**



Modified Lee Symptom Scale (mLSS): a 28-item instrument with 7 subscales (skin, eyes, mouth, lung, nutrition, energy and psych) containing 2–7 items which allow calculation of a summary score.

Axatilimab is Well-Tolerated at 0.3mg/kg Q2W

	Axatilimab 0.3 mg/kg Q2W n=79	Axatilimab 1.0 mg/kg Q2W n=81	Axatilimab 3.0 mg/kg Q4W n=79
Axatilimab dose changes owing to AE, n (%)			
Discontinuation	5 (6.3)	18 (22.2)	14 (17.7)
Dose decrease	5 (6.3)	6 (7.4)	13 (16.5)
Any grade AE in ≥20% of total patients			
Fatigue	18 (22.8)	16 (19.8)	21 (26.6)
Headache	15 (19.0)	14 (17.3)	16 (20.3)
Periorbital edema	2 (2.5)	19 (23.5)	23 (29.1)
COVID-19	13 (16.5)	18 (22.2)	11 (13.9)
Laboratory-based abnormalities			
AST increase	11 (13.9)	31 (38.3)	43 (54.4)
CPK increase	9 (11.4)	26 (32.1)	49 (62.0)
Lipase increased	9 (11.4)	21 (25.9)	39 (49.4)
Lactate dehydrogenase increased	11 (13.9)	22 (27.2)	32 (40.5)
ALT increase	10 (12.7)	18 (22.2)	31(39.2)
Amylase increase	3 (3.8)	10 (12.3)	34 (43.0)
At least 1 related Grade ≥3 AE, n (%)	14 (17.7)	28 (34.6)	37 (46.8)
Fatal AE	1 (1.3)	7 (8.6)	6 (7.6)

Axatilimab is a Novel Therapeutic Option for Patients with cGVHD

- ✓ Primary endpoint met across all treatment doses
- ✓ Highest ORR and least toxicity at 0.3 mg/kg Q2W dose
- ✓ Responses achieved across all patient subgroups, regardless of prior treatment
- ✓ Axatilimab treatment of patients with recurrent/refractory cGVHD had robust clinical activity and durable responses
- ✓ AEs were consistent with reported vulnerabilities of patients with advanced cGVHD or on-target macrophage depletion

Next Steps

- BLA submission by year-end 2023; approval anticipated in 2024
- Initiation of Phase 2 study evaluating axatilimab in combination with ruxolitinib in 2024
- Initiation of Phase 3 study evaluating axatilimab in combination with steroids in 2024

Q&A

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