INCYTE AT ASH 2022

Discovering New Targets for the Treatment of MPNs

DECEMBER 11, 2022

FORWARD LOOKING STATEMENTS

Except for the historical information set forth herein, the matters set forth in this presentation contain predictions, estimates, and other forward-looking statements, such as statements regarding Incyte's opportunities to drive growth and diversification and Incyte's LIMBER program, including Incyte's expectations regarding ongoing clinical trials and clinical trials to be initiated, and the potential treatment benefits as well as the potential for market growth represented by such studies.

These forward-looking statements are based on the Company'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; the effects of the COVID 19 pandemic and measures to address the pandemic on the Company's clinical trials, supply chain and other third-party providers, sales and marketing efforts and business, development and discovery operations; determinations made by the FDA and other regulatory agencies both inside and outside of the United States; the Company's dependence on its relationships with and changes in the plans of its collaboration partners; the efficacy or safety of the Company's products and the products of the Company's collaboration partners; the acceptance of the Company's products and the products of the Company's collaboration partners in the marketplace; market competition; unexpected variations in the demand for the Company's products and the products of the Company's collaboration partners; the effects of announced or unexpected price regulation or limitations on reimbursement or coverage for the Company's products and the products of the Company's collaboration partners; sales, marketing, manufacturing and distribution requirements, including the Company'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; and other risks detailed from time to time in the Company's reports filed with the Securities and Exchange Commission, including its quarterly report on Form 10 Q for the quarter ended September 30, 2022. The Company disclaims any intent or obligation to update these forward-looking statements.

AGENDA & WELCOME

STEVEN STEIN, MD

CHIEF MEDICAL OFFICER, INCYTE

Incyte | SOLVE ON.

Incyte Representation at ASH

57	1	15	33
Abstracts Accepted	**Oral Plenary**	**Oral Presentations**	**Poster Presentations**

64TH ASH ANNUAL MEETING AND EXPOSITION • NEW ORLEANS, LOUSIANA

DECEMBER 10-13, 2022

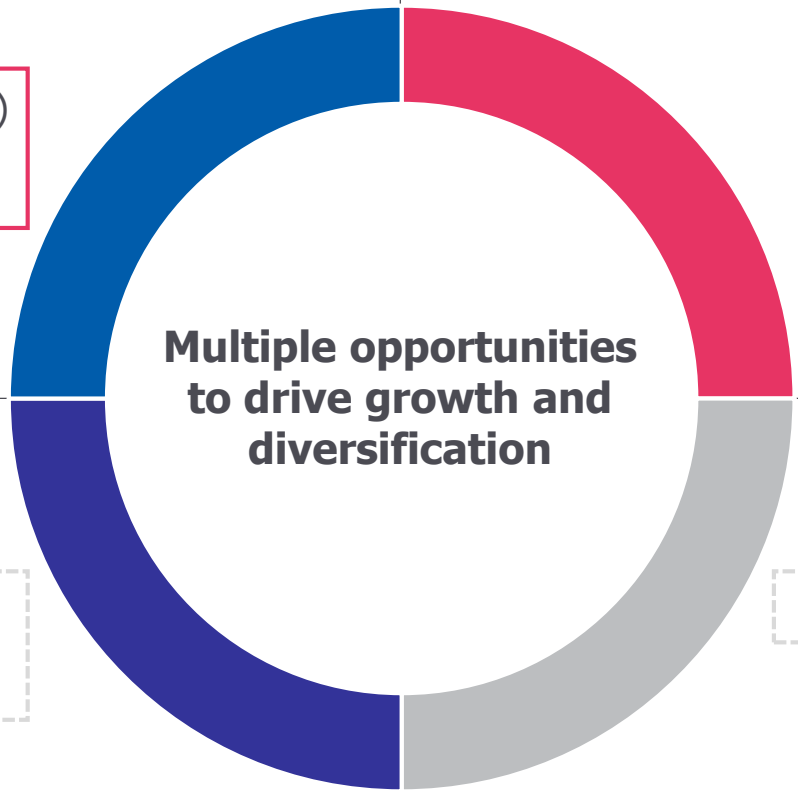
8 abstracts are publication only.

MPNs and GVHD (LIMBER*)

- JAKAFI® (ruxolitinib)
- QD ruxolitinib
- Combinations (PI3Kδ, BET, ALK2)
- INCA33989 (mCALR)
- axatilimab
- Novel targets

Dermatology

- OPZELURA™ (ruxolitinib) cream
- povorcitinib
- auremolimab



Hematology/Oncology

- MONJUVI® (tafasitamab-cxix)
- PEMAZYRE® (pemigatinib)
- parsaclisib in AIHA
- INCB99280 & '318 (oral PD-L1)
- retifanlimab

Royalties

- JAKAVI® (ruxolitinib)
- TABRECTA® (capmatinib)
- OLUMIANT® (baricitinib)

*LIMBER = Leadership in MPNs and GVHD Beyond Ruxolitinib

Jakavi (ruxolitinib) licensed to Novartis ex-US, Tabrecta (capmatinib) licensed to Novartis worldwide, Olumiant (baricitinib) licensed to Lilly worldwide; these brands are trademarks of Novartis (Jakavi and Tabrecta) and Lilly (Olumiant). Iclusig (ponatinib) is a registered trademark of ARIAD. Monjuvi (tafasitamab-cxix) is a registered trademark of MorphoSys. Development of axatilimab in collaboration with Syndax Pharmaceuticals.

Agenda

MULTIPLE OPPORTUNITIES TO EXPAND LEADERSHIP IN MYELOPROLIFERATIVE NEOPLASMS (MPNs)

8:00-8:45 pm	Steven Stein, MD	**Welcome and Introduction**
	Srdan Verstovsek, MD, PhD	**Myeloproliferative Neoplasms (MPNs): Treatment and Novel Therapeutics in Development**
	Abdulraheem Yacoub, MD	**parsaclisib** (PI3Kδ) **+ ruxolitinib** (JAK1/JAK2) Phase 2 study in MF patients with suboptimal response to ruxolitinib
	Peter Langmuir, MD	**INCB00928** (ALK2), **INCB57643** (BET) Combination opportunities with ruxolitinib
	Patrick Mayes, PhD	**INCA33989** (mCALR) Development of anti mutant-CALR mAb as potential treatment for MF and ET
8:45-9:10 pm	**Q&A**	

Myeloproliferative Neoplasms (MPNs)

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

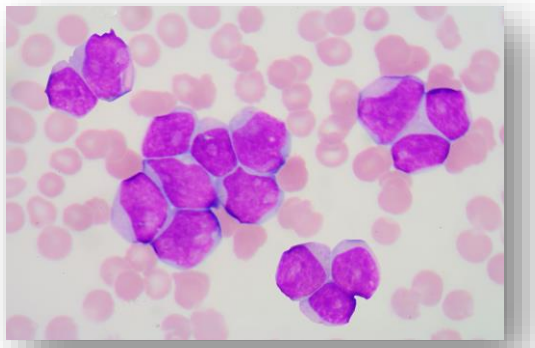
Srdan Verstovsek, MD, PhD
Professor of Medicine, Department of Leukemia
University of Texas MD Anderson Cancer Center
Houston, Texas, USA

Hallmarks of Myelofibrosis

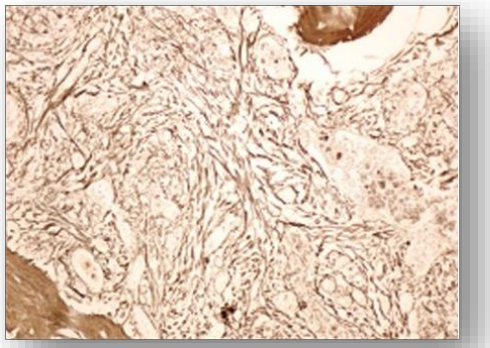
Increased JAK/STAT signaling[1]

- **Myeloproliferation[2]**
- **Abnormal levels of cytokines[2]**

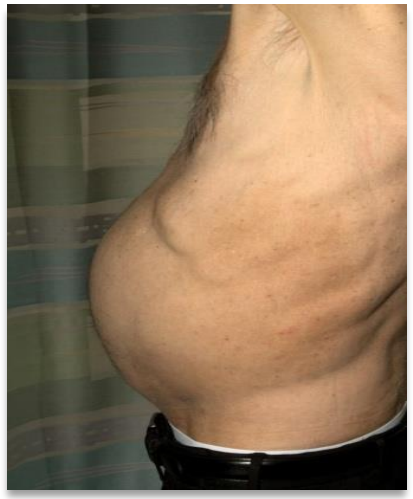
Abnormal blood counts



Bone marrow fibrosis[5]



Extramedullary hematopoiesis (splenomegaly)



MF-associated symptom burden[3,4]

- Abdominal pain and discomfort
- Bloating, early satiety, and cachexia
- Pruritis
- Night sweats
- Fatigue
- Weight loss
- Bone and joint pain
- Shortness of breath

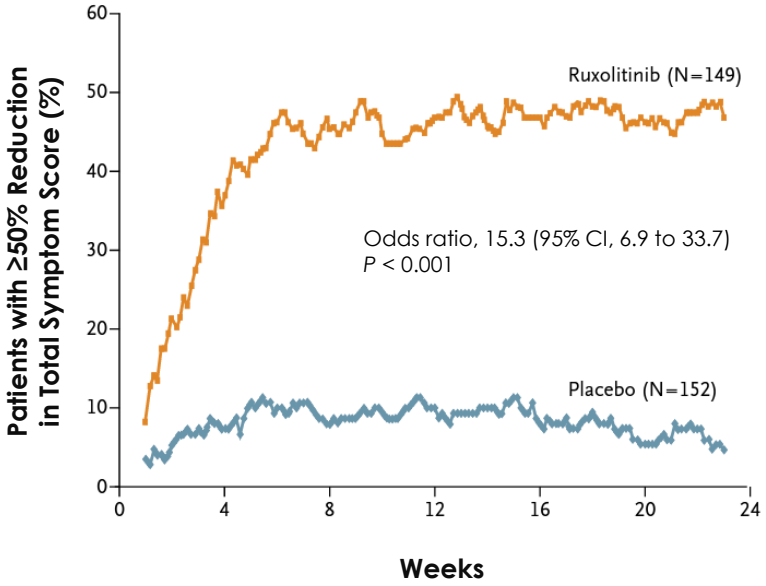
1. Quintás-Cardama A, et al. *Nat Rev Drug Discov*. 2011;10(2):127-140. 2. Spivak JL. *N Engl J Med*. 2017;376(22):2168-2181. 3. Mesa RA, et al. *Cancer*. 2007;109(1):68-76. 4. Scherber R. *Blood*. 2011;118(2):401-408. 5. Cervantes F, et al. *Blood*. 2009;113(13):2895-2901. 5. Image courtesy of Akpınar TS, et al. *Turk J Haematol*. 2013;30(1):8-12.

Key Myelofibrosis Treatment Goals

- Improve symptoms
- Reduce splenomegaly
- Alleviate anemia

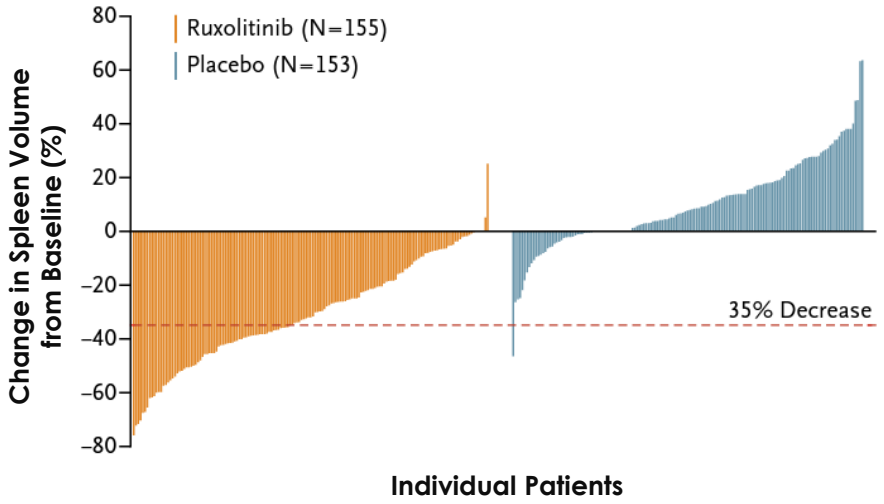
Ruxolitinib in COMFORT-I

Improvement in Symptom Burden[1]



Changes in Spleen Volume[1]

(Baseline to Week 24)



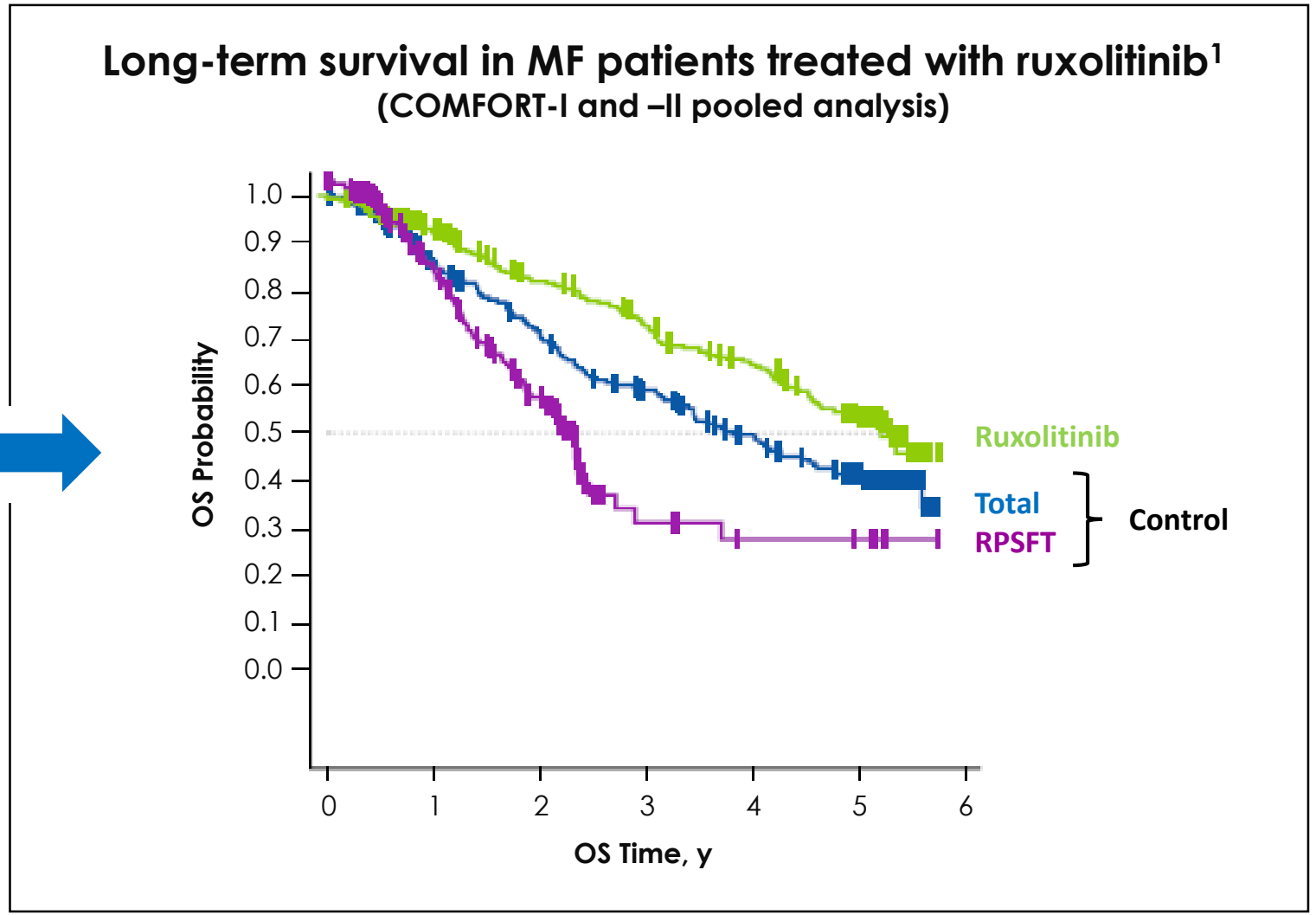
1. Verstovsek S, et al. N Engl J Med. 2012;366(9):799-807.

Ultimate Goal of Improving Overall Survival in Myelofibrosis

Improve overall survival

	Ruxolitinib (n=301)	Control (n=227) RPSFT	Total
Median OS, y	5.3	2.3	3.8

HR, 0.35 (95% CI, 0.23-0.59)



RPSFT= Rank-preserving structural failure time

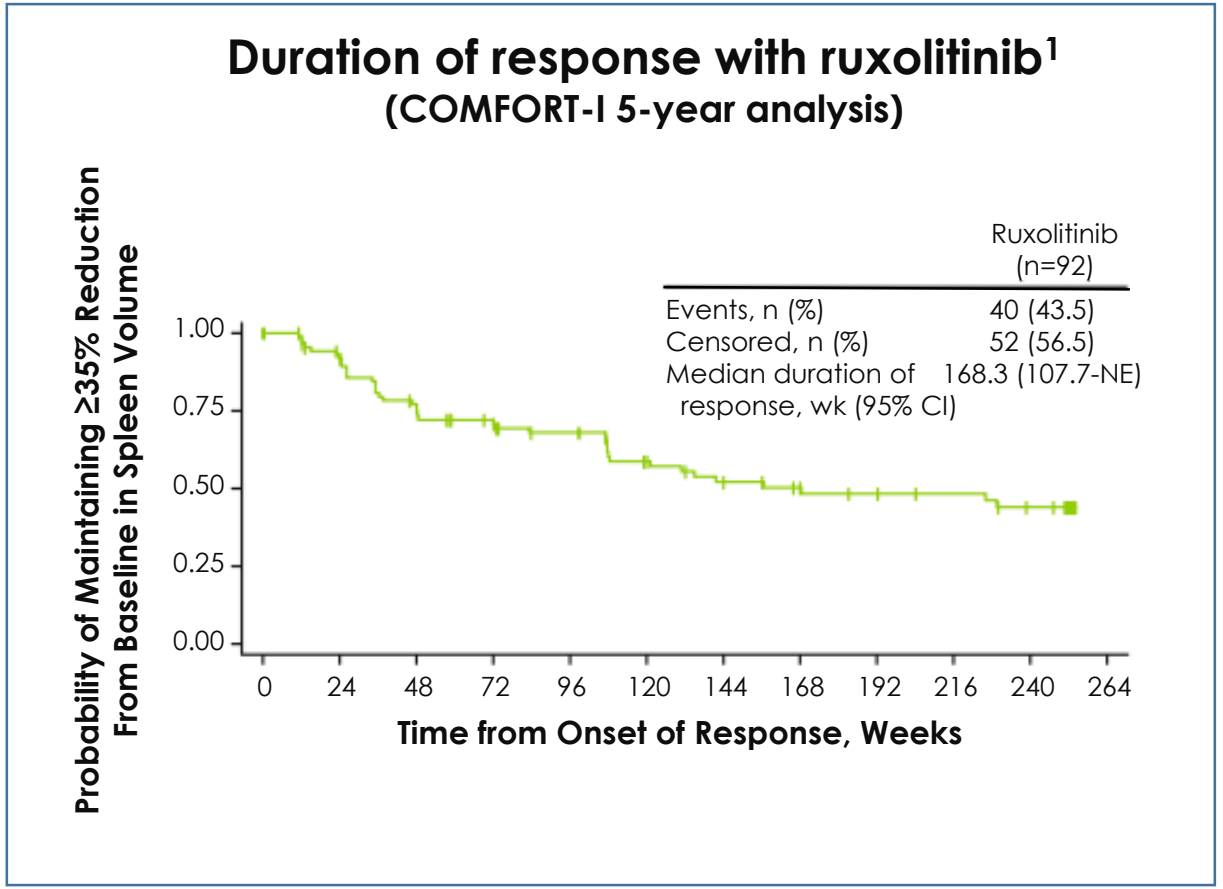
1. Adapted from Verstovsek S, et al. J Hematol Oncol. 2017;10:156.

Where are the Unmet Needs in Myelofibrosis Treatment?

Disease progression / Lack or loss of ruxolitinib response

Management of anemia

Need for therapies that will achieve PR and CR



1. Adapted from Verstovsek S, et al. J Hematol Oncol. 2017;10:156.

Duration of ≥35% reduction from baseline in spleen volume. Duration of spleen response was evaluated for the 92 patients in the ruxolitinib group who achieved a ≥35% reduction from baseline in spleen volume. NE, not evaluable

Addressing Unmet Needs with Novel Targets in Development for MF

Disease progression / Lack or loss of ruxolitinib response

- **PI3Kδ inhibition:** potential synergies with co-targeting PI3Kδ and JAK2 signaling

- **BET inhibition:** BET proteins regulate NF-kB, which are important drivers of pro-inflammatory cytokine expression and bone marrow fibrosis in MF

Management of anemia

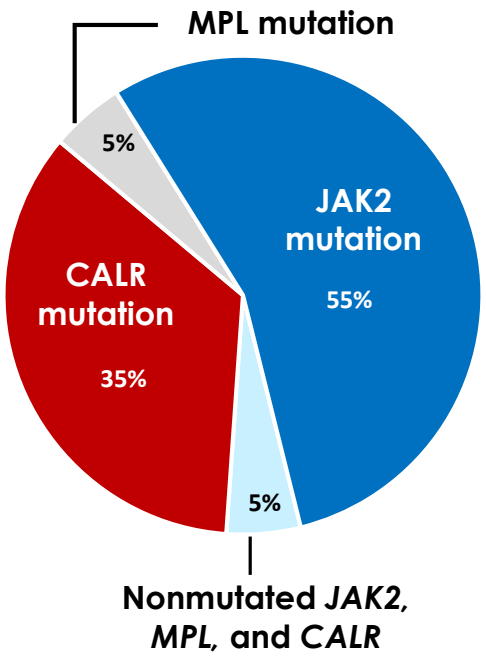
- **ALK2 inhibition:** ALK2 associated with elevated hepcidin, which may contribute to anemia and is associated with increased transfusion rate and reduced overall survival

Need for therapies that will achieve PR and CR

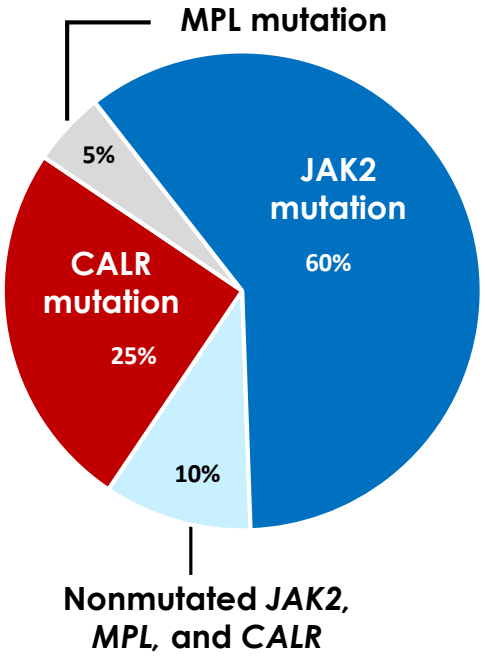
- **mCALR blockade:** mCALR drives oncogenic transformation which drives enhanced megakaryopoiesis and proplatelet formation

CALR mutations in Philadelphia Chromosome-Negative MPNs

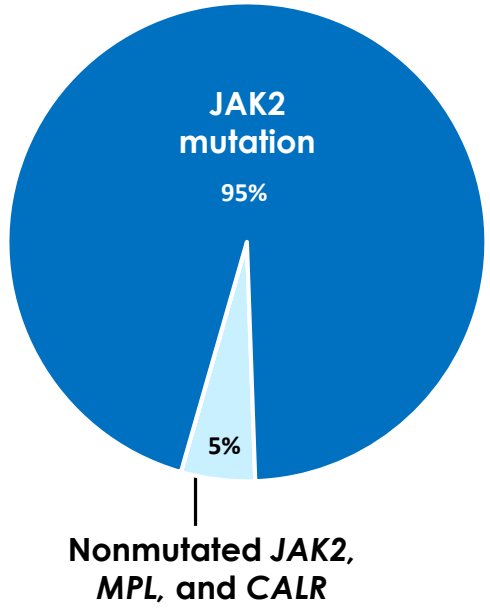
Primary Myelofibrosis (N=203)



Essential Thrombocythemia (N=311)



Polycythemia vera (N=382)



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

Hematologic Features and Epidemiology of ET

- ET is a classic MPN of the bone marrow that manifests itself with elevated platelets, sometimes with elevated WBC, enlarged spleen and systemic symptoms.

Incidence:

~1.5 cases per 100,000[1]

Prevalence:

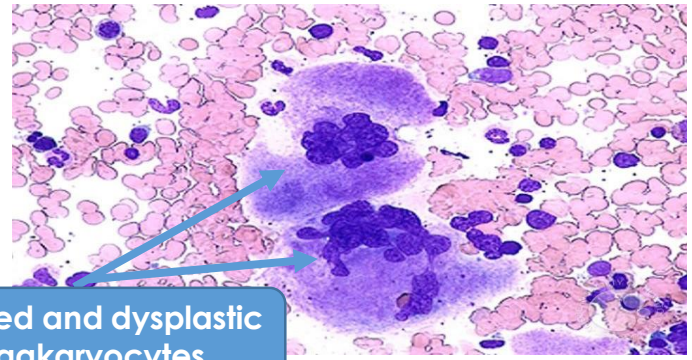
~30 cases per 100,000[2]

Within 10 years:

~4% of patients progress to MF and

~1.4% progress to AML[3,4]

Megakaryocyte Dysplasia in a Patient Diagnosed With ET[5]



AML= Acute myeloid leukemia.

1. Blood Journal 2015. 2. Briere, J. Orphanet Journal of Rare Diseases. 2007. 3. Finazzi G, et al. Blood. 2005;105(7):2664-2670. 4. Abdel-Wahab OI, Levine RL. Annu Rev Med. 2009;60:233-245. 5. American Society of Hematology Image Bank. http://imagebank.hematology.org/image/2736/essential-thrombocythemia--2?type=upload. Accessed on September 29, 2017.

ET: Revised IPSET-Thrombosis Prognostic Score for Int/High-risk

Risk Factors	
Age ≥60 years	
Previous thrombosis	
JAK2V617F mutation positive	
Risk Categories	
Intermediate-risk: Age ≥60 years only	**---------- aspirin, NO cytoreduction**
High-risk: Previous thrombosis OR ≥60 years and *JAK2V617F*	**---------- aspirin and cytoreduction**

UNMET NEEDS

Need for therapies that will achieve PR and CR, and not only reduce thrombotic risk and symptoms, but eliminate risk for progression to MF and AML

Barbui T, et al. Blood Cancer 2015;5:e369;
Haider M, et al., Am J Hematol 2016;91(4):390-394.

Novel Agents in Development to Help Improve Outcomes for ET Patients

Ropeginterferon
- Phase 3

Pelabresib (BETi)
- Phase 2

Bomedemstat (LSD1)
- Phase 2

Mutant CALR-peptide based vaccine
- Phase 1

INCA33989 (mCALR mAb)
- Entering clinic in 2023

Conclusion

- Ruxolitinib is the standard of care in treating MF
  - Reduces spleen volume, improves symptom burden and is the only therapy with long-term survival data
- However, MF is a progressive disease and therapies are needed to address unmet needs (disease progression, loss of response, anemia)
- Novel targets in development (PI3Kδ, BET, ALK2) all have potential to improve upon safety or efficacy of SOC
- Mutant-CALR mAb has the potential to be disease modifying but still early in development

Parsaclisib + ruxolitinib in myelofibrosis

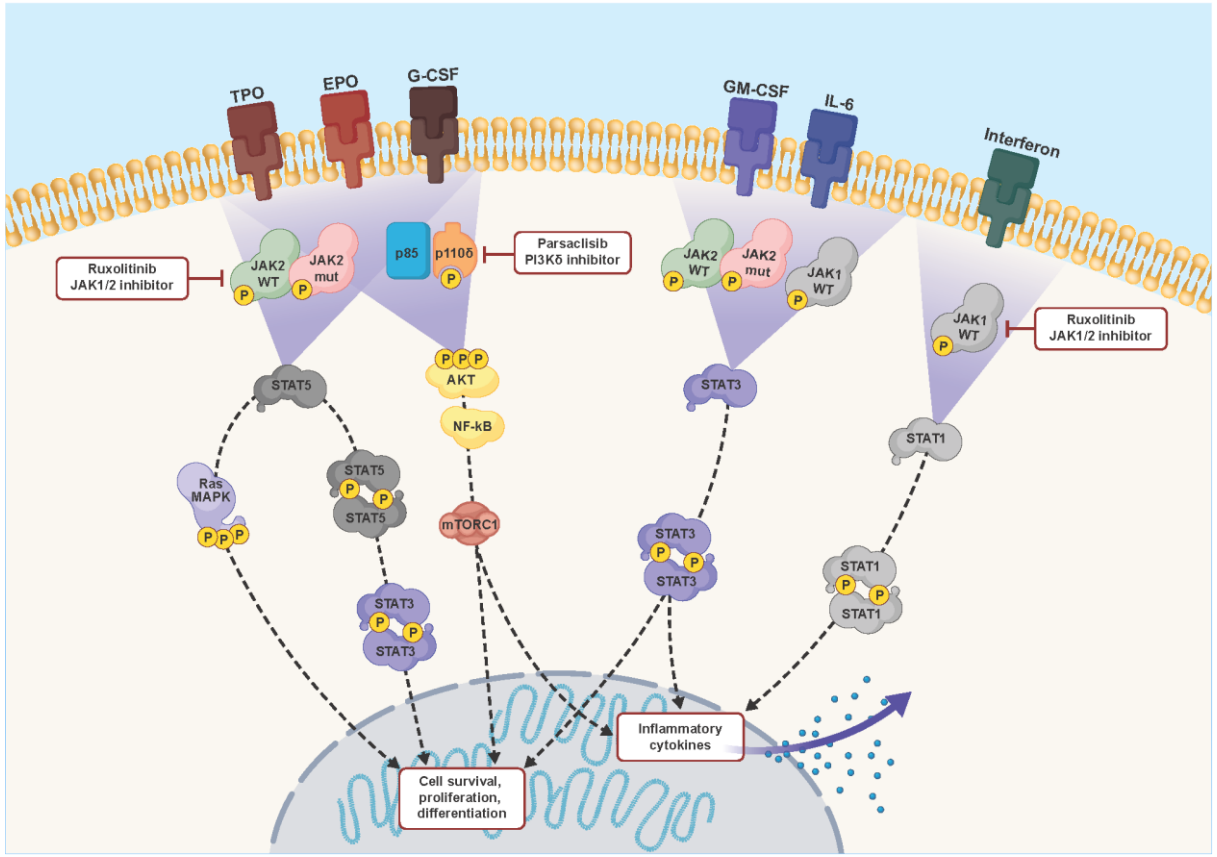
Abdulraheem Yacoub, MD

Associate Professor

Hematologic Malignancies and Cellular Therapeutics

University of Kansas Cancer Center

JAK1/2 and PI3K Pathways in Myelofibrosis



Adapted from "Pathogenesis of Myeloproliferative Neoplasms: Role and Mechanisms of Chronic Inflammation" by Hermouet S, et al. Mediators Inflamm. 2015;2015:145293 is licensed under CC BY 3.0 (https://creativecommons.org/licenses/by/3.0/) and Targeting the PI3K pathway in myeloproliferative neoplasms, Gerds AT et al., Expert Rev Anticancer Ther, 2022, Published by Informa UK Limited, trading as Taylor & Francis Group. Reprinted by permission of the Informa UK Limited trading as Taylor & Francis Ltd, http://www.tandfonline.com

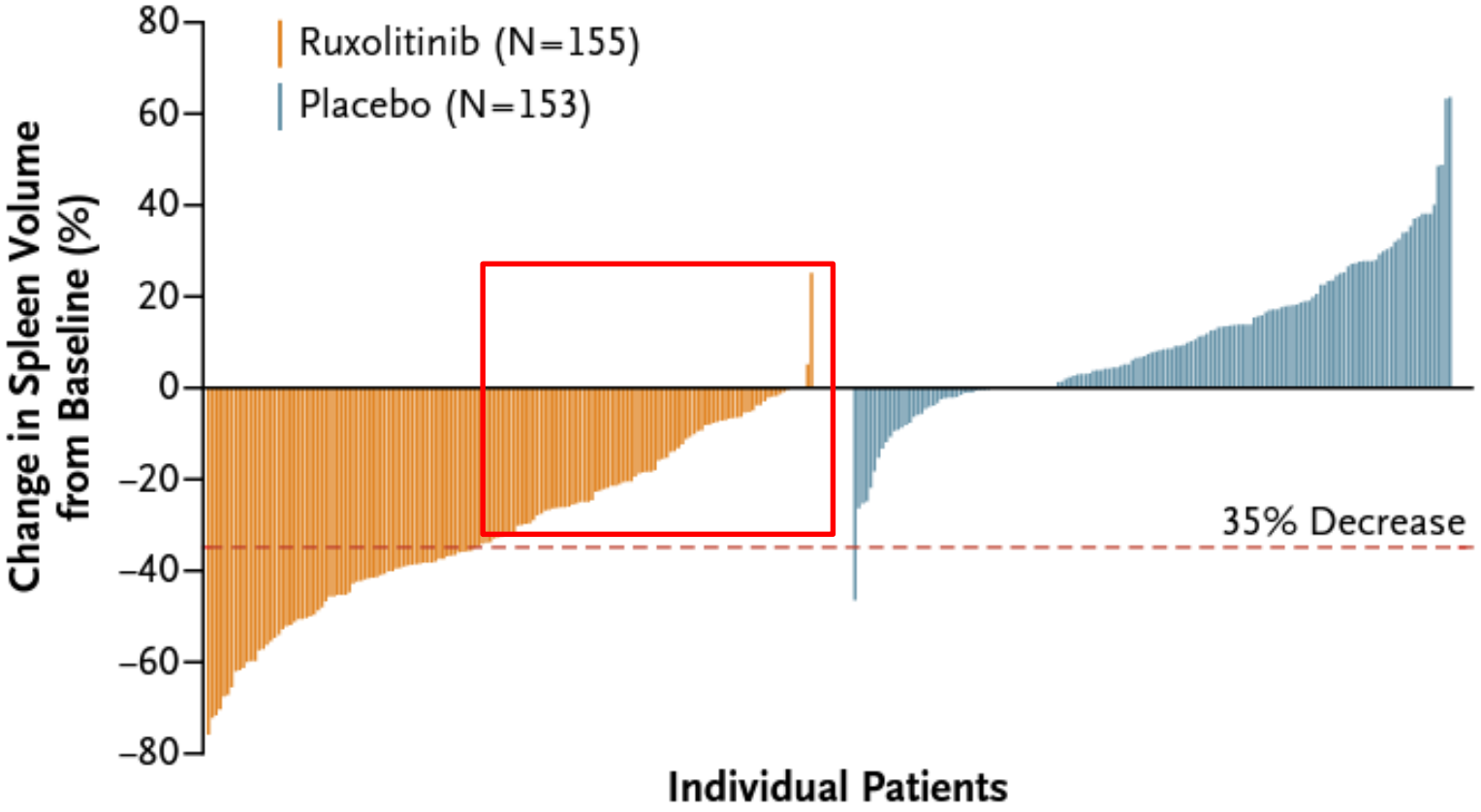
- Ruxolitinib, a potent JAK1/2 inhibitor, reduces spleen volume, improves symptoms, and prolongs survival in patients with intermediate- or high-risk MF[1-3]
- Suboptimal responses may occur in a subset of patients, possibly due to continued signaling via the PI3K pathway[4-6] while receiving treatment with JAK inhibitors
- Parsaclisib, a potent and highly selective next-generation PI3Kδ inhibitor, exhibits favorable pharmacokinetics for once-daily dosing[7]
- Combined inhibition of JAK1/2 and PI3K signaling pathways may improve outcomes in MF[6]

JAK, Janus kinase; MF, myelofibrosis; PI3K, phosphatidylinositol 3-kinase.

1. Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807. **2.** Harrison C, et al. *N Engl J Med.* 2012;366:787-798. **3.** Cervantes F, et al. *Blood.* 2013;122:4047-4053. **4.** Grimwade L, et al. *Br J Haematol.* 2009;147:495-506. **5.** Oku S, et al. *Br J Haematol.* 2010;150:334-344. **6.** Gerds AT, et al. *Expert Rev Anticancer Ther.* 2022;22:835-843. **7.** Shin N, et al. *J Pharmacol Exp Ther.* 2020;374:211-222.

Significant need for add-on therapy to ruxolitinib in MF patients

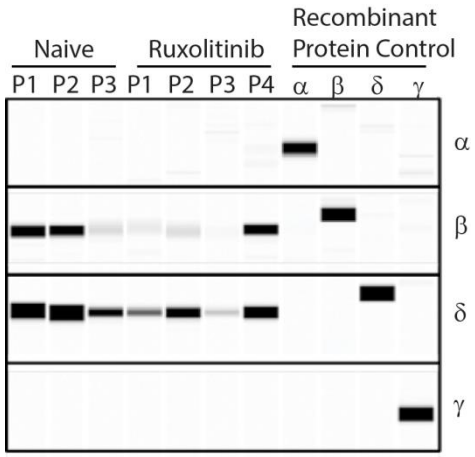
Changes in Spleen Volume (Baseline to Week 24)
(COMFORT-I)



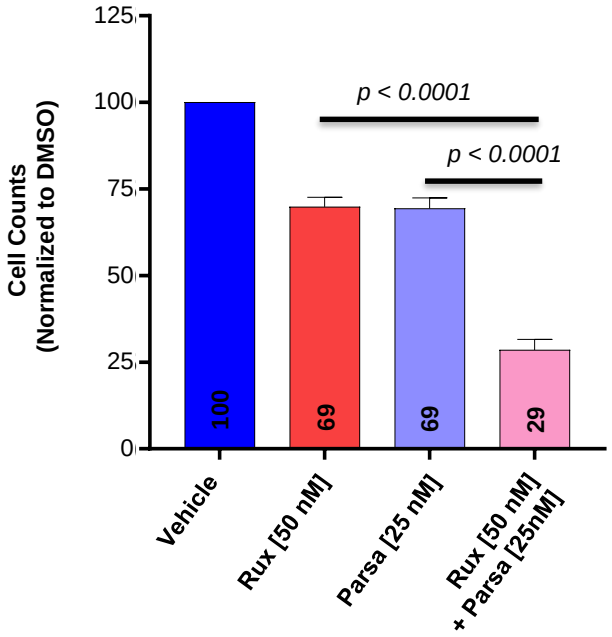
Verstovsek S, et al. N Engl J Med. 2012;366(9):799-807.

Rationale for combining a PI3Kδ inhibitor with ruxolitinib

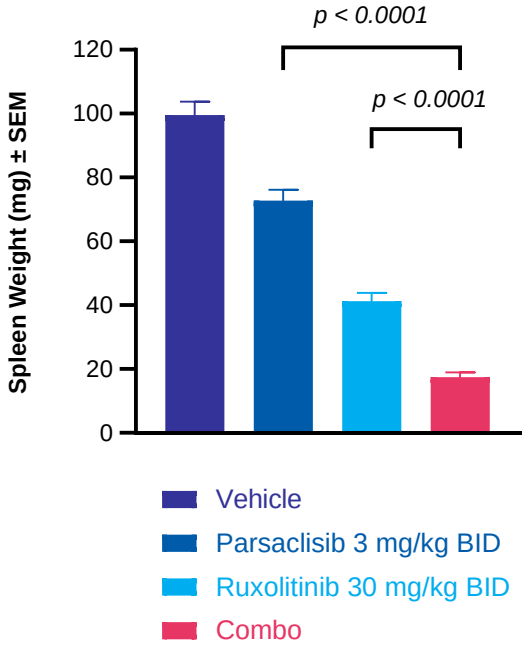
PI3Kd is the predominant PI3K isoform expressed in CD34+ cells from MF patients, and PI3Kd signaling is attenuated with a PI3Kd inhibitor[1]



Synergy of parsaclisib + ruxolitinib combination seen with effect on MF CD34+ cells



Combined inhibition of PI3K/AKT and JAK/STAT pathways demonstrates synergy in the JAK2V617F knock-in mouse model of MPN



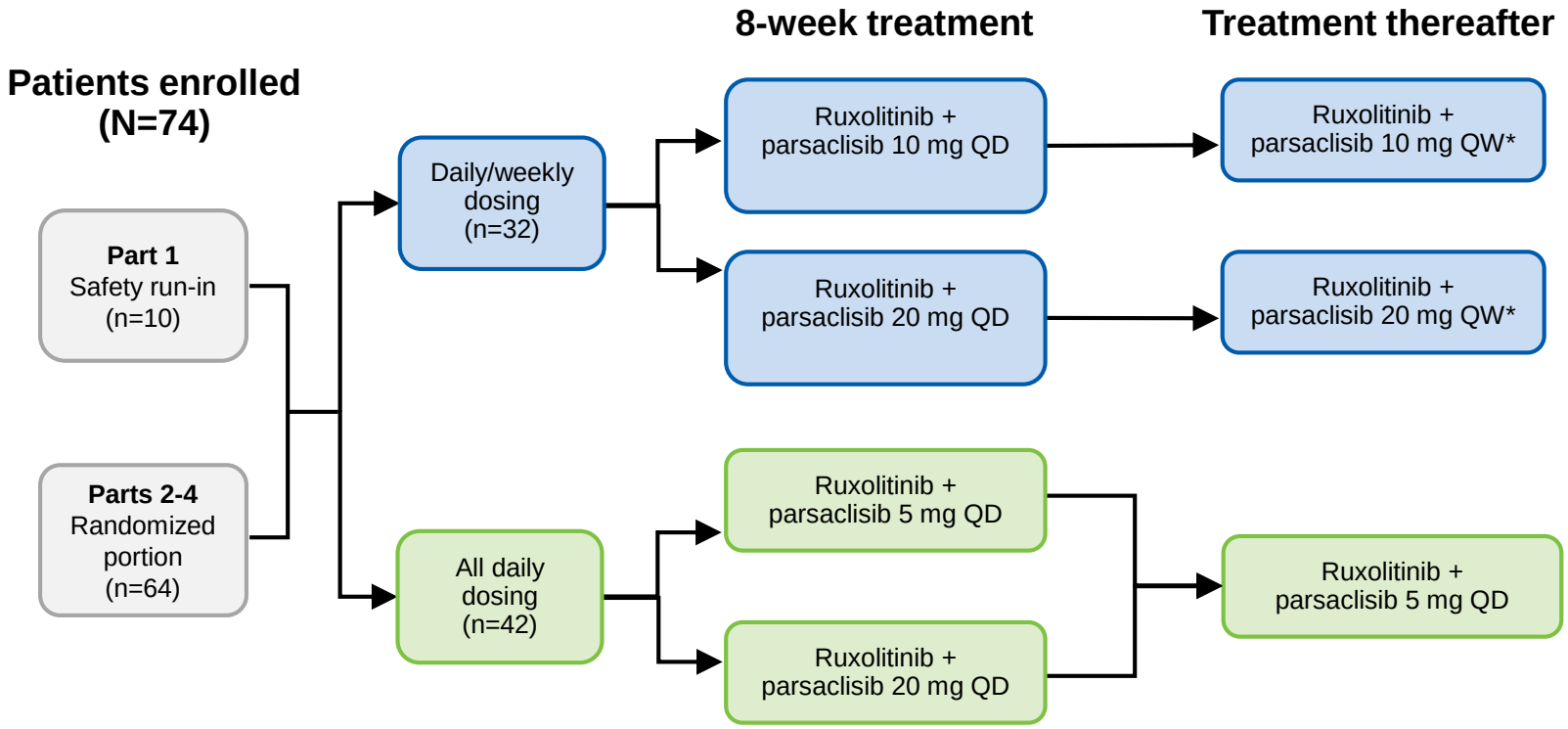
Data on file, Incyte. One-way ANOVA with Tukey's multiple comparisons test

1. Meadows et al., Blood, 2013.

Parsaclisib add-on in MF patients on stable-dose ruxolitinib; no washout period

Key Inclusion Criteria

- ≥18 years of age
- Primary or secondary MF
- Ruxolitinib (5-25mg BID) for ≥6 months with stable dose for ≥8 weeks prior to enrollment
- Suboptimal response to ruxolitinib monotherapy[1]
- Platelet count ≥50×10^9/L in the 4 weeks before screening
- Study had no exclusion criteria for anemia or transfusion dependence



Primary endpoint: Change in spleen volume (Baseline to week 12)

Secondary endpoint: Change in spleen volume to week 24, change in spleen length, change in total symptom score, and safety

Secondary MF includes: PET-MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis.
[1]Suboptimal response defined as: Palpable spleen >10 cm below LSM on physical examination at screening OR Palpable spleen 5-10 cm below LSM on physical examination AND active symptoms of MF at the screening defined as 1 symptom score ≥5 or 2 symptom scores ≥3 each, using the Screening Symptom Form (10-point scale for each of the 7 symptoms. Symptoms include night sweats, pruritus, abdominal discomfort, pain under left ribs, early satiety, bone/muscle pain, and inactivity. *Options for QD dosing were made available to patients once daily dosing regimens were added to the protocol. QD, once daily; QW, once weekly.
Adapted from Yacoub, et al, ASH 2022.

Baseline Characteristics

Characteristic	All Daily Group (n=42)
Age, median (range), y	69 (51-84)
Male, n (%)	20 (48)
Time since initial diagnosis, median (range), mo	37.5 (4.9-251.5)
Ruxolitinib use, median (range) Daily dose, mg Duration, mo	 29.3 (8.7-44.8) 16.4 (5.1-105.5)
Patients with palpable spleen, n (%) Median length (range), cm	42 (100) 11 (5-30)
Spleen volume, median (range), cm^3	1878 (434-3904)
MFSAF-TSS, median (range)	16.3 (0.6-38.4)
MPN-SAF-TSS, median (range)	30.0 (3.0-65.0)
Hemoglobin, median (range), g/L	97.5 (57-155)
DIPSS risk level at baseline, n (%) High / Intermediate-2 / Intermediate-1 / Low	 10 (24) / 19 (45) / 12 (29) / 1 (2)
MF subtype, n (%) PMF / PPV-MF / PET-MF	 23 (55) / 12 (29) / 7 (17)

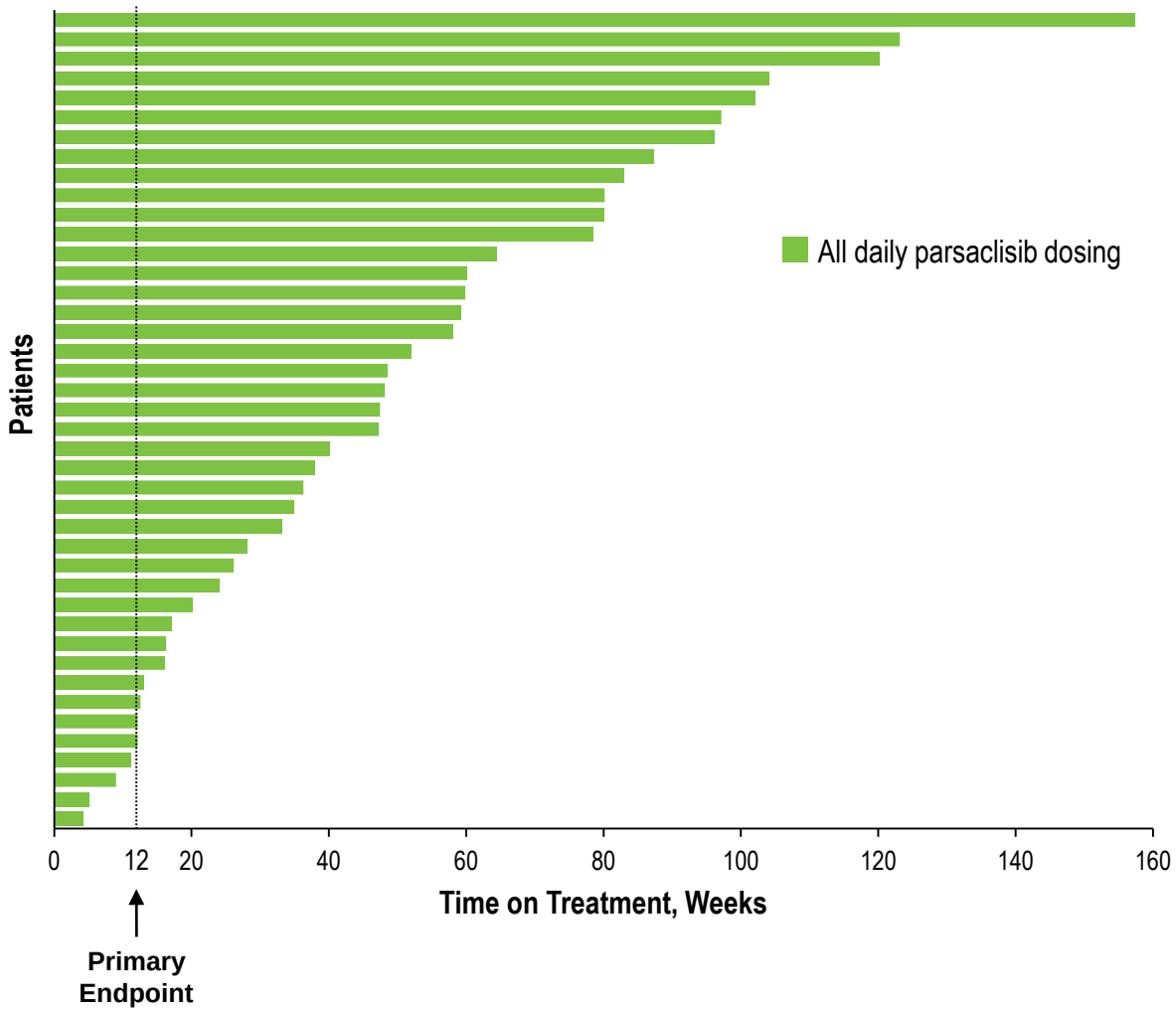
At baseline, patients had enlarged spleens and high symptom burden despite ruxolitinib treatment

- Ruxolitinib daily dose: 29.3 mg/day (median)
- Enlarged spleen volume: 1878 cm^3 (median)
- High symptom burden: MFSAF-TSS 16.3 (median)
- No exclusion criteria for:
  - Transfusion dependence
  - Anemia

DIPSS= Dynamic International Prognostic Scoring System; TSS= total symptom score.
Adapted from Yacoub, et al, ASH 2022.

Results

Duration of Treatment



All-Daily Dosing (n=42)

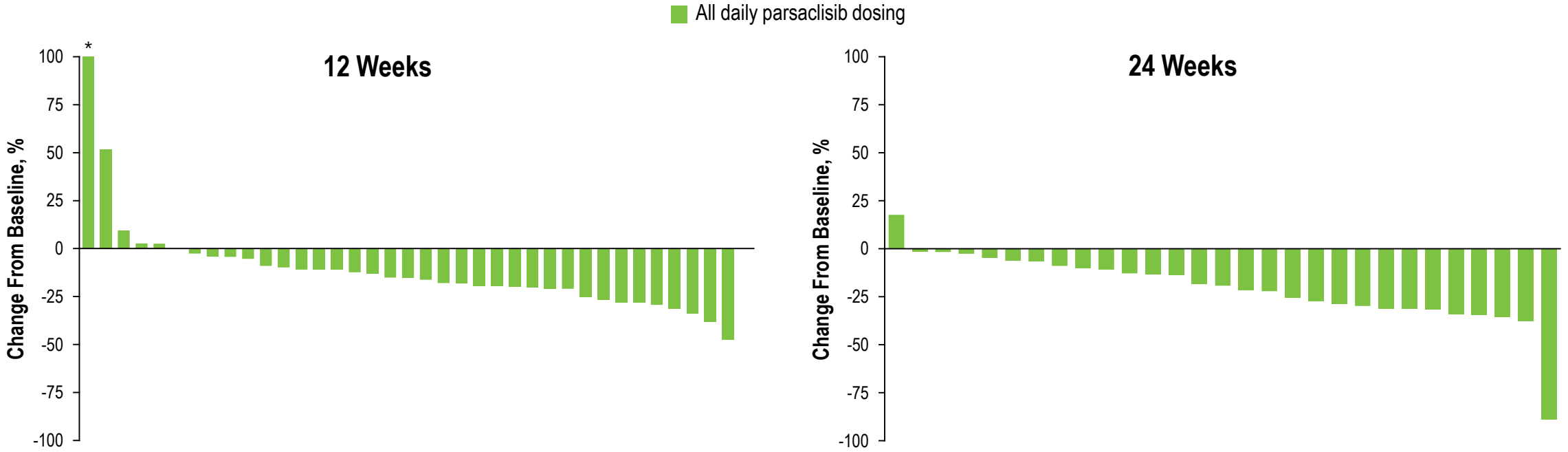
- Median treatment duration was 47.4 weeks
- Median daily dose:
  - 5.0 mg/d for parsaclisib
  - 29.2 mg/d for ruxolitinib
- After the study was ended, 13 patients (31%) from All daily arm continued to an open-label study of parsaclisib

Length of Time Patients Received Treatment
(All daily arm), n (%)

≥12 Weeks	≥1 Year	≥2 Years
38 (90%)	17 (40%)	3 (7%)

Adapted from Yacoub, et al, ASH 2022.

Percentage Change in Spleen Volume and Response Categories at 12 and 24 Weeks

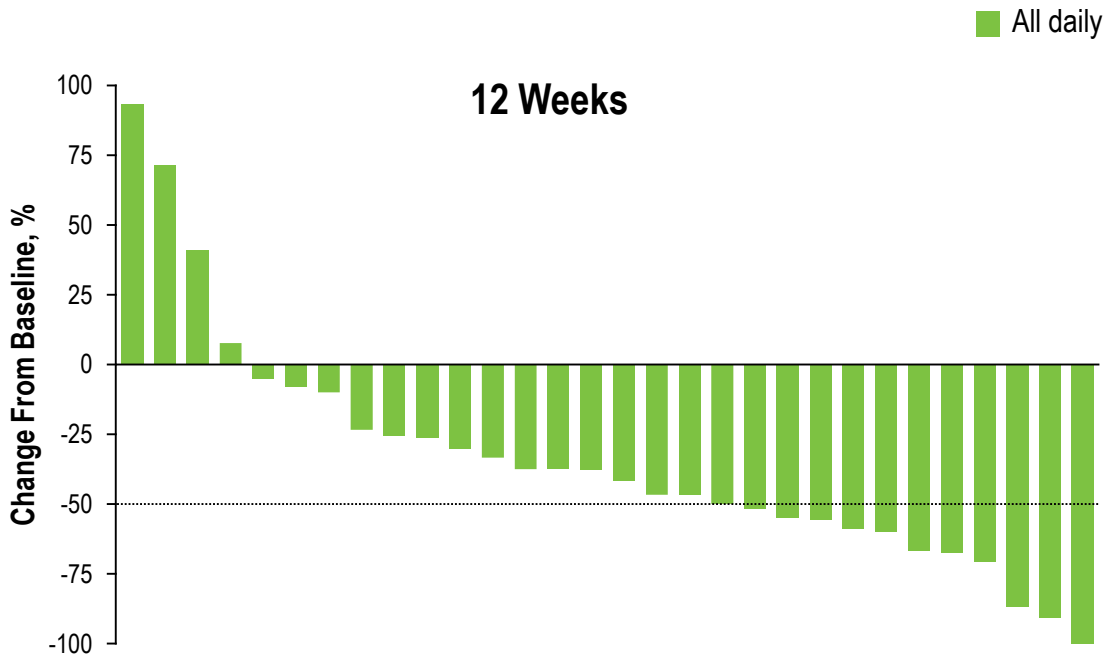


Response Category, n (%)	All Daily Dosing
Week 12	n=42
≥10% reduction	25 (59.5)
≥25% reduction	9 (21.4)
≥35% reduction	2 (4.8)

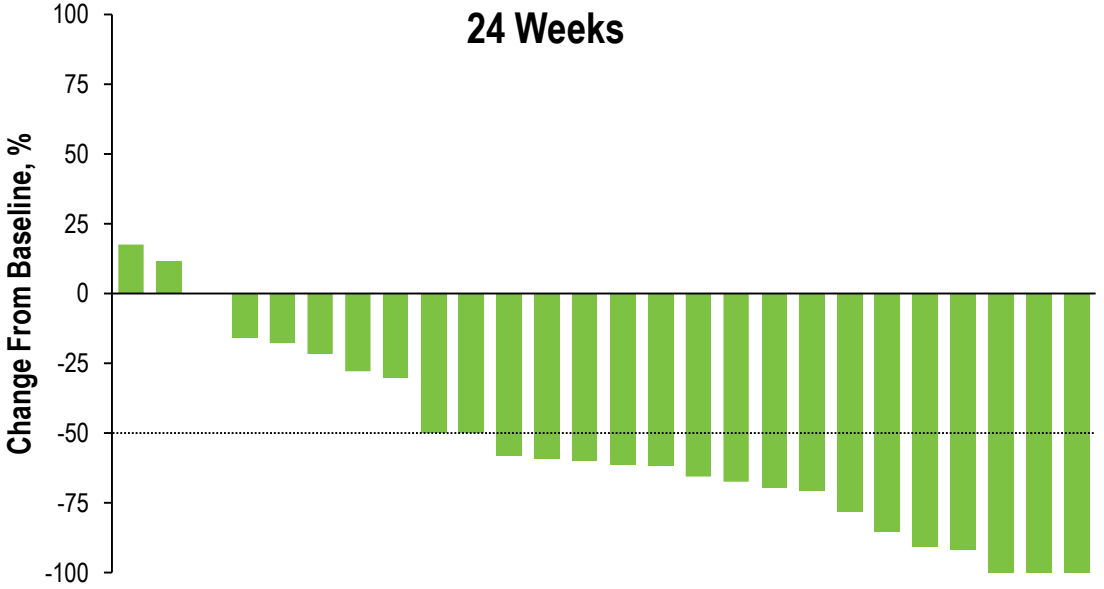
Response Category, n (%)	All Daily Dosing
Week 24	n=42
≥10% reduction	21 (50.0)
≥25% reduction	12 (28.6)
≥35% reduction	3 (7.1)

*Patient had best percentage change from baseline to >100%.
Adapted from Yacoub, et al, ASH 2022.

Change in MPN-SAF Symptom Score and Response Categories at 12 and 24 Weeks



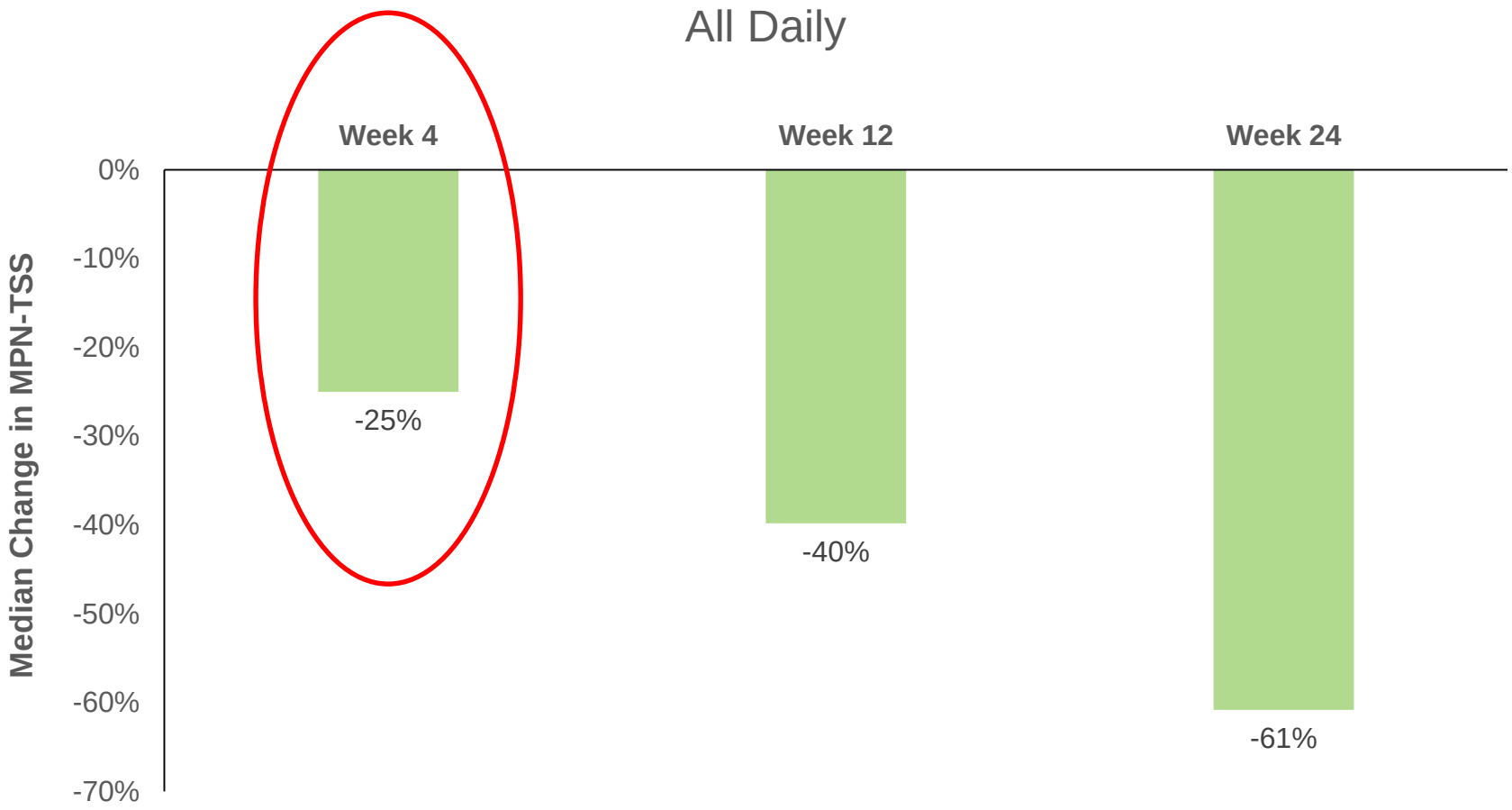
Median Change in MPN-TSS at 12 Weeks	n	% Change (Range)
All daily dosing	30	-39.8 (-100.0 to 93.3)
Proportion Reaching 50% Decrease in TSS		**n/N (%)**
All daily dosing	37	12/37 (32.4)



Median Change in MPN-TSS at 24 Weeks	n	% Change (Range)
All daily dosing	26	-60.8 (-100.0 to 17.5)
Proportion Reaching 50% Decrease in TSS		**n/N (%)**
All daily dosing	37	18/37 (48.6)

Adapted from Yacoub, et al, ASH 2022.
MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; TSS, total symptom score.

Change in MPN-SAF Symptom Score at 4 Weeks



Data on file, Incyte.

Treatment Emergent Adverse Events (TEAEs)

New-Onset Thrombocytopenia (All Daily Dosing)

	Worst Abnormal Value on Study				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
n (%)	9 (21)	10 (24)	9 (21)	11 (26)	3 (7)

- 7/11 patients with new-onset grade 3 entered the study at grade 2
- 1/3 patients with new-onset grade 4 entered the study at grade 2
- Thrombocytopenia led to parsaclisib discontinuation in 2 (4.8%) patients in the all daily dosing cohort

TEAEs of Special Interest (All Daily Dosing)

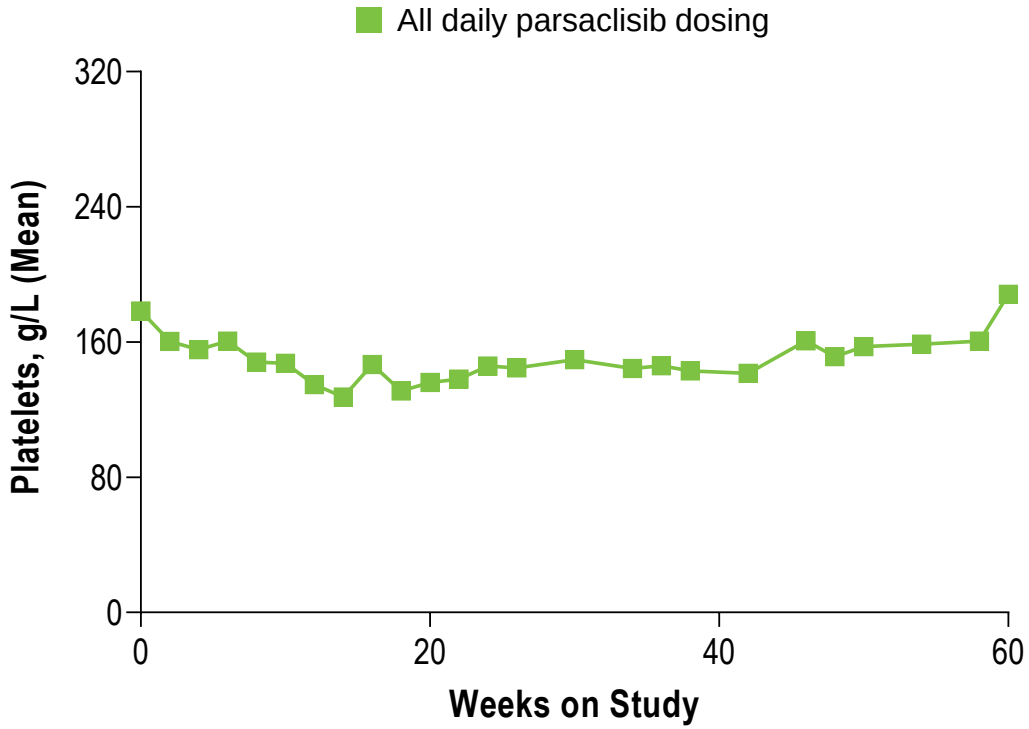
Event, n (%)	All Daily Dosing (n=42)
Grade ≥2 diarrhea	0
Grade ≥3 ALT increase	0
Grade ≥3 AST increase	0
Grade ≥2 rash	0
Herpes simplex*	2 (4.8)
VZV infection	2 (4.8)
Colitis	0
Pneumonitis	0

- No Grade ≥2 diarrhea or colitis

Adapted from Yacoub, et al, ASH 2022.
*Includes herpes simplex, oral herpes, and genital herpes.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; VZV, varicella zoster virus.

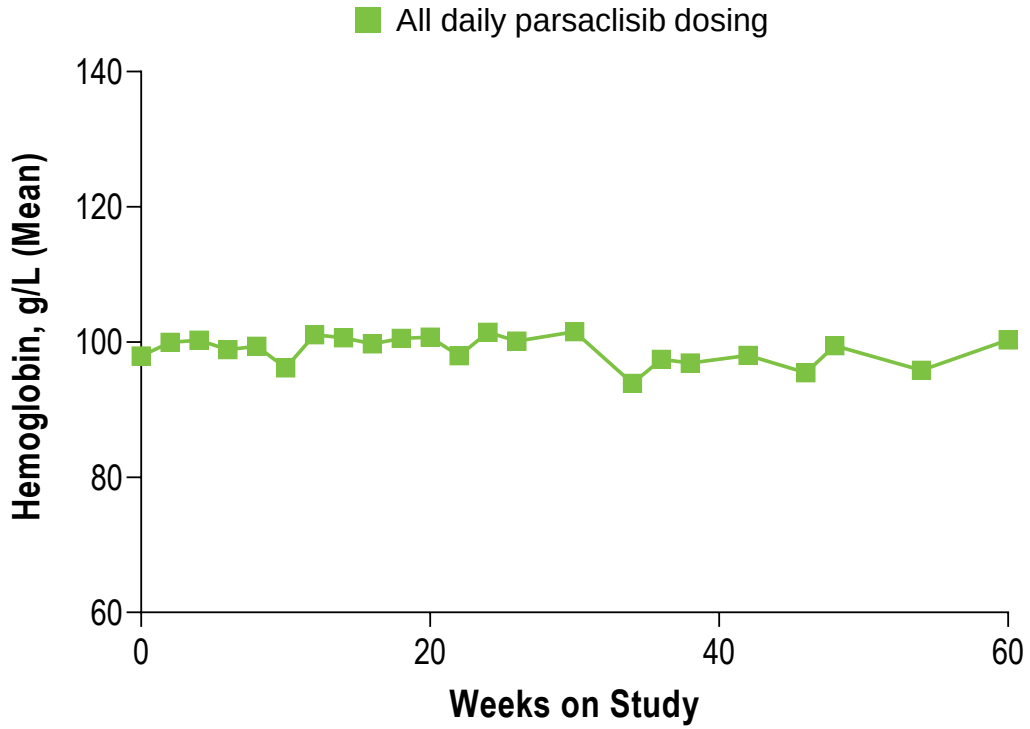
Hematologic TEAEs (Laboratory Assessment): Platelet and Hemoglobin Levels

Platelet Levels



- Platelet levels remained steady over time
  - Study had no exclusion for transfusion dependence

Hemoglobin Levels



- Hemoglobin levels remained steady over time
  - Study had no exclusion criteria for anemia

Adapted from Yacoub, et al, ASH 2022.

Conclusions

- **Add-on parsaclisib in patients with MF with suboptimal response to ruxolitinib resulted in:**
  - Additional SVR and improvement in symptom burden
  - Limited grade 3 or 4 adverse events and TEAE-related discontinuations
  - TEAEs common to PI3K in lymphoma (eg. hepatitis, rash, colitis) were infrequent with the addition of parsaclisib
- **Ruxolitinib dose was not interrupted; no washout (be careful with cross trial comparisons!)**

- **Parsaclisib + ruxolitinib combination is being evaluated in two phase 3 trials; patients with low platelets are included in both studies**
  - LIMBER-304: MF patients with suboptimal response to ruxolitinib
  - LIMBER-313: 1L MF study

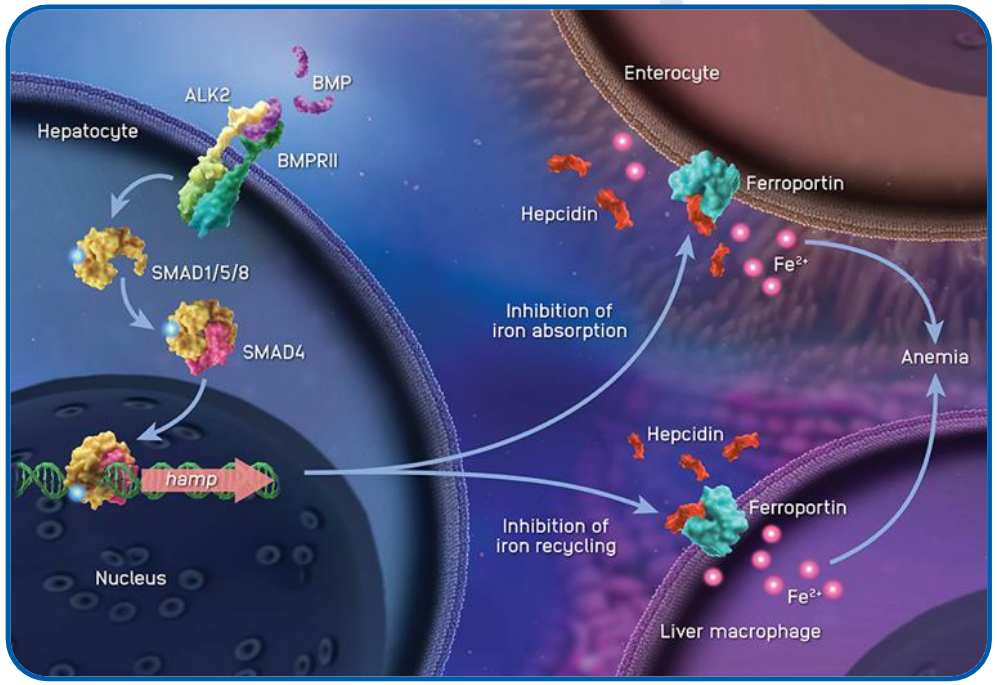
INCB00928 (ALK2) + RUXOLITINIB

PETER LANGMUIR, MD

GVP, ONCOLOGY TARGETED THERAPEUTICS

ALK2 mechanism of action: Therapeutic hypothesis to target anemia

- In MF patients, elevated plasma hepcidin is correlated with higher risk scores and is associated with/predicts decreased survival in MF[1,2,3]
- Elevated cytokine levels in conditions like MF stimulate excess hepcidin production[4]
- Excess plasma hepcidin inhibits iron recycling, which limits erythropoiesis and contributes to development of anemia[5]
- INCB00928 binding to ALK2 should downregulate hepcidin expression, mobilize iron for erythropoiesis and improve anemia



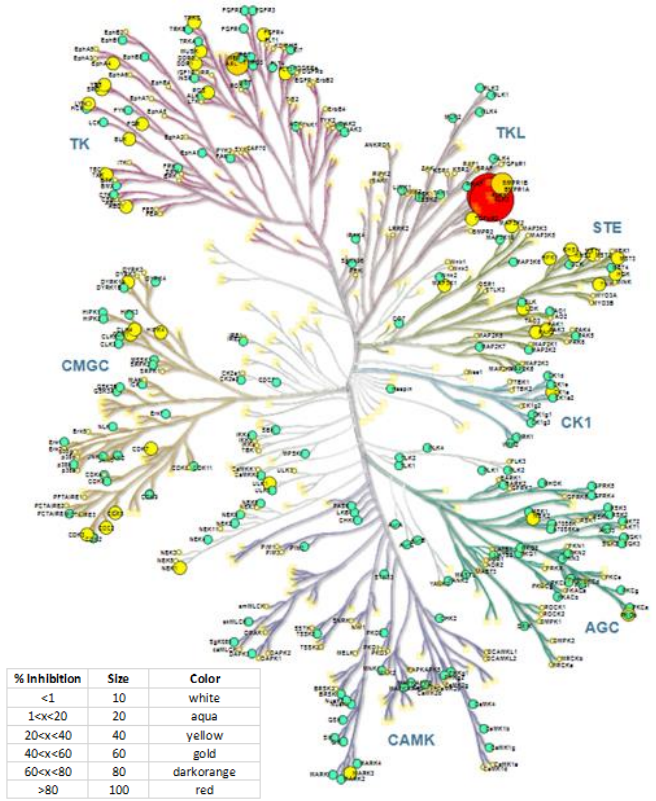
INCB00928 (ALK2)
+
Ruxolitinib (JAK1/2)

Potential to:

- Alleviate, lessen 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.

INCB00928 is a potent and selective ALK2 inhibitor



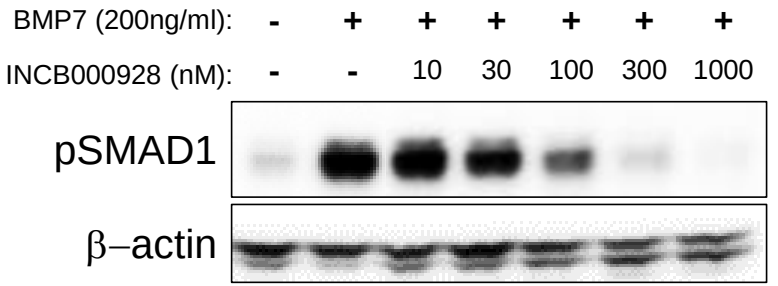
% Inhibition	Size	Color
<1	10	white
1<x<20	20	aqua
20<x<40	40	yellow
40<x<60	60	gold
60<x<80	80	darkorange
>80	100	red

Illustration reproduced courtesy of Cell Signaling Technology

INCB00928 is a selective inhibitor of ALK2 kinase activity

	ALK2	ALK1	ALK3	ALK5	ALK6
Fold selectivity vs ALK2	1x	14x	53x	262x	208x

ALK2i potently inhibits BMP7-induced SMAD phosphorylation in human hepatocytes



pSMAD1 IC_{50}: 83 nM

Adapted from Chen Y, et al. ASH 2020. Poster 3095. IC50, half maximal inhibitory concentration.

INCB00928 (ALK2) ± ruxolitinib: Dose escalation and dose expansion

TGA: INCB00928 monotherapy

- MF diagnosis
- TD or symptomatic anemia
- Resistant, refractory, lost response to, or intolerant/ineligible for JAKi

Dose Escalation

Starting dose, 50mg QD

Identify RDE(s)

Dose Expansion

n ≥ 9 patients

TGB: INCB00928 + ruxolitinib

- MF diagnosis
- TD or symptomatic anemia
- Stable dose of ruxolitinib ≥12 wks

Dose Escalation

Starting dose, 100mg QD

Identify RDE

Dose Expansion

n = 25 patients

Adapted from Mohan, et al., ASH 2022.

TD = transfusion dependent; JAK = Janus kinase; RDE = recommended dose for expansion; TGA = treatment group A; TGB = treatment group B.

INCB00928 (ALK2) ± ruxolitinib: Baseline characteristics

- 18 patients enrolled
  - Monotherapy (TGA): 14 patients
  - Combination (TGB): 4 patients

- Patients at baseline:
  - High hepcidin levels
  - Anemic
  - Majority were transfusion dependent

	TGA				TGB
	50 mg qd (n=4)	100 mg qd (n=4)	200 mg qd (n=6)	Total (n=14)	100 mg qd + Ruxolitinib (n=4)
Age, median (range), y	73.5 (53–84)	63.0 (60–72)	70.5 (63–75)	70.0 (53–84)	75.5 (68–79)
Men, n (%)	3 (75.0)	2 (50.0)	4 (66.7)	9 (64.3)	2 (50.0)
Race, n (%)					
White	4 (100)	2 (50.0)	4 (66.7)	10 (71.4)	2 (50.0)
Black	0	1 (25.0)	0	1 (7.1)	0
Asian	0	1 (25.0)	2 (33.3)	3 (21.4)	0
Other	0	0	0	0	2 (50.0)
Time since first MF diagnosis, median (range), y	4.2 (2.6–10.3)	3.0 (0.2–8.1)	2.1 (0.6–23.1)	2.7 (0.2–23.1)	11.6 (9.3–14.3)
DIPSS risk level, n (%)					
High	0	0	1 (16.7)	1 (7.1)	1 (25.0)
Intermediate-2	4 (100)	4 (100)	5 (83.3)	13 (92.9)	3 (75.0)
Prior MF therapy, n (%)					
Ruxolitinib	4 (100)	2 (50.0)	5 (83.3)	11 (78.6)	4 (100)
Other	2 (50.0)	2 (50.0)	3 (50.0)	7 (50.0)	3 (75.0)
Transfusion dependent,* n (%)	3 (75.0)	2 (50.0)	4 (66.7)	9 (64.3)	1 (25.0)
Hb, median (range),† g/dL	8.3 (7.0–8.7)	7.4 (6.4–8.3)	7.5 (6.6–9.2)	7.7 (6.4–9.2)	8.3 (7.9–8.7)
Hepcidin, median (range),‡ ng/mL	374 (318–535)	158 (85–275)	133 (79–275)	235 (79–535)	157 (6.9–250)

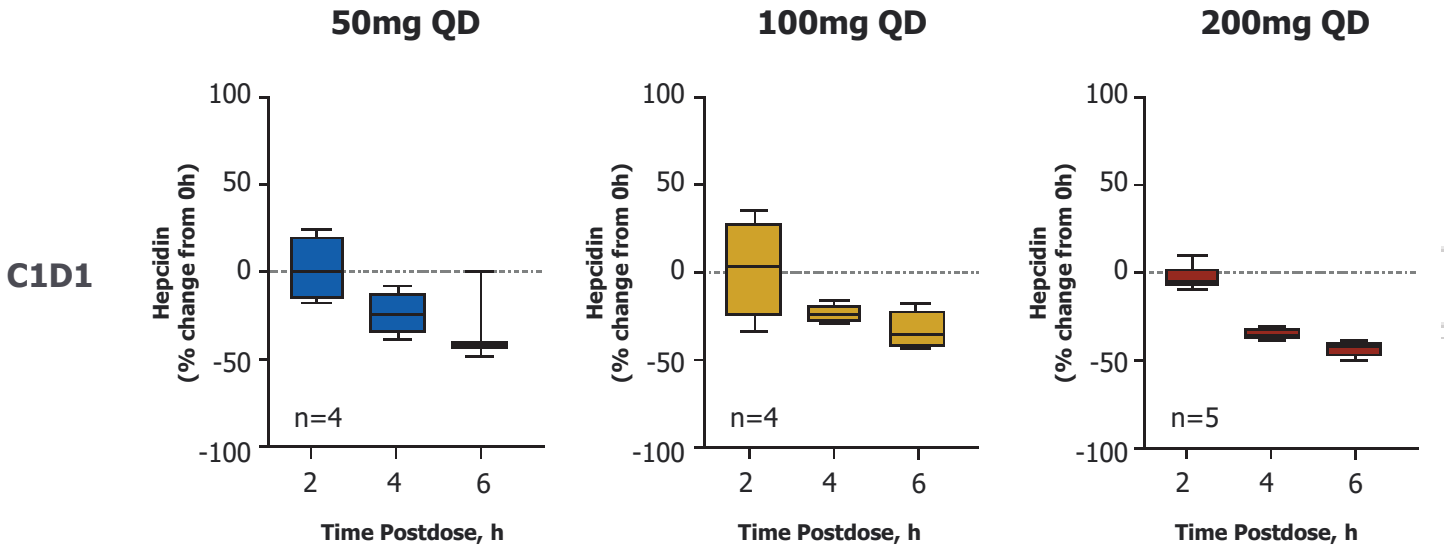
Adapted from Mohan, et al., ASH 2022.
DIPSS, Dynamic International Prognostic Scoring System; Hb, hemoglobin; MF, myelofibrosis; qd, once daily; RBC, red blood cell; TGA, treatment group A; TGB, treatment group B.
* Defined as patients who have received ≥4 units of RBC transfusions during the 28 days before C1D1, or have received ≥4 units of RBC in the 8 weeks before C1D1 for an Hb level of <8.5 g/dL in the absence of bleeding or treatment-induced anemia; the most recent transfusion must have occurred within 28 days before C1D1.
† 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.

INCB00928 (ALK2) monotherapy reduces hepcidin levels

- INCB00928 monotherapy **reduced hepcidin** (at all dose levels tested)
- One patient on INCB00928 200mg QD achieved initial **anemia response**[1]

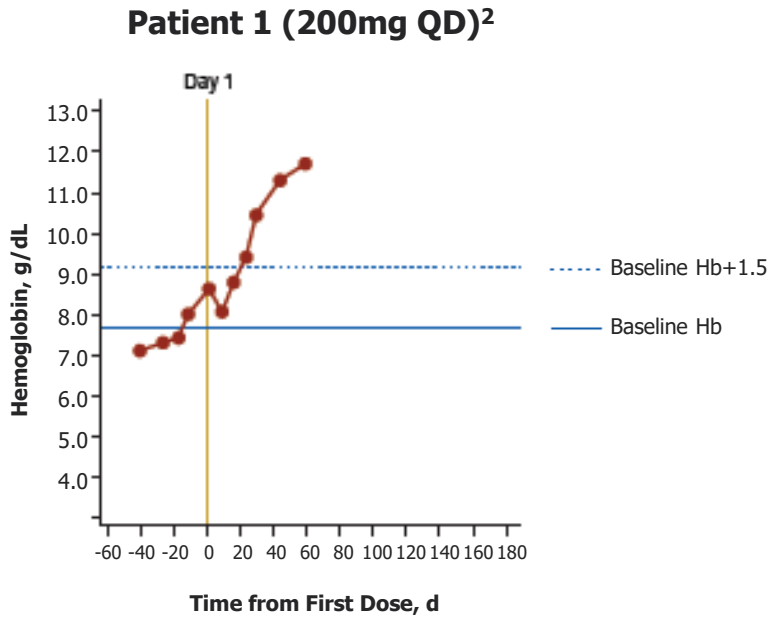
Changes in hepcidin levels following INCB00928 dosing

(INCB00928 monotherapy; TGA)



Hemoglobin over time in anemia responder

(200mg INCB00928 monotherapy; TGA)



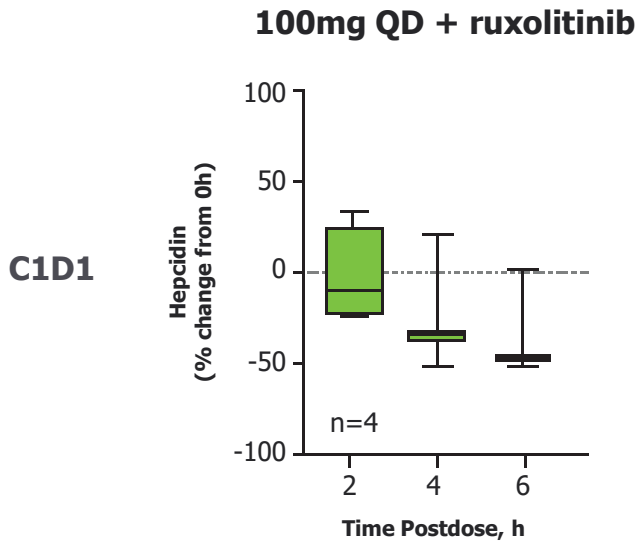
Adapted from Mohan, et al., ASH 2022.
C1D1, Cycle 1 Day1; QD = once daily; TGA = treatment group A; TGB = treatment group B
1. Anemia response = Hgb increase ≥1.5 g/dL vs baseline
2. Protocol defined endpoint of 12 weeks for anemia response not yet reached at time of data cut-off; patient continues on study

INCB00928 (ALK2) + ruxolitinib: Early signals of clinical activity

- Greatest hepcidin reductions were observed at 100mg INCB00928 + ruxolitinib (TGB)
- Two patients (out of 4) on 100mg INCB00928 + ruxolitinib achieved initial **anemia response**[1]

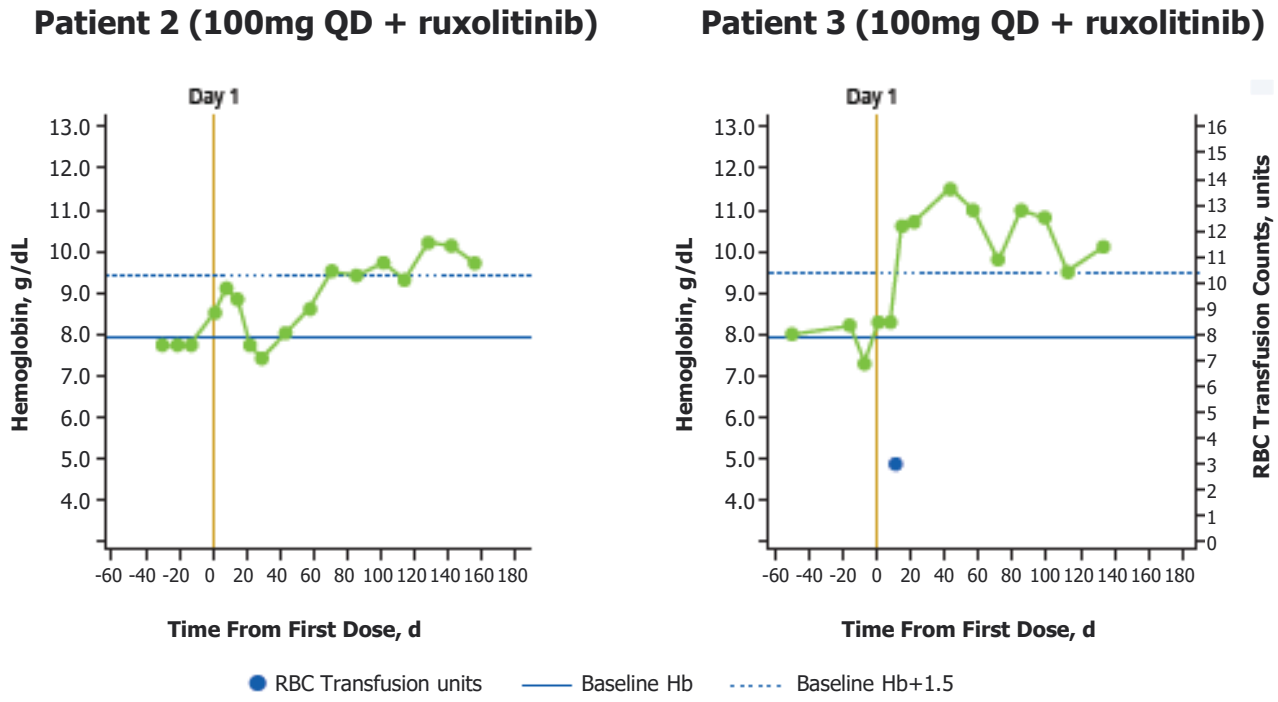
Changes in hepcidin levels following INCB00928 dosing

(100mg INCB00928 + ruxolitinib; TGB)



Hemoglobin over time in anemia responders[2]

(100mg INCB00928 + ruxolitinib; TGB)



Adapted from Mohan, et al., ASH 2022.
C1D1, Cycle 1 Day1; QD = once daily; TGA = treatment group A; TGB = treatment group B
1. Anemia response = Hgb increase ≥1.5 g/dL vs baseline
2. Protocol defined endpoint of 12 weeks for anemia response not yet reached at time of data cut-off; both patients continue on study

INCB00928 (ALK2) ± ruxolitinib: Favorable safety profile to date

- No DLTs occurred in either treatment group
- No TRAEs led to study drug discontinuation
- Predominantly Grade 1/2 treatment-emergent AEs; few grade ≥3 TRAEs observed

All Grade 3/4 Treatment-Emergent Adverse Events

	TGA				TGB
Event, n (%)*	50 mg qd (n=4)	100 mg qd (n=4)	200 mg qd (n=6)	Total (n=14)	100 mg qd + Ruxolitinib (n=4)
Thrombocytopenia	1 (25.0)	0	1 (16.7)	2 (14.3)	0
COVID-19	0	0	1 (16.7)	1 (7.1)	0
Neutropenia	0	0	1 (16.7)	1 (7.1)	0
Pneumonia	1 (25.0)	0	0	1 (7.1)	0

INCB00928 was well tolerated in prior studies in healthy volunteers

	Single-dose	10-day dose
N	91	56
Max dose tested	500 mg QD	300 mg BID
Results	Well tolerated; No DLTs	
MTD	Not reached	

Data on file, Incyte.

Adapted from Mohan, et al., ASH 2022.
DLT = dose-limiting toxicity; qd = once daily; TGA = treatment group A; TGB = treatment group B.

INCB00928 (ALK2) ± ruxolitinib: Conclusion

- Reduction in postdose hepcidin levels observed at all dose levels tested
- Improvements in anemia observed in both monotherapy and combination cohorts
- INCB00928 monotherapy or in combination with ruxolitinib was generally well-tolerated
  - Predominantly grade 1/2 TEAEs
  - No DLTs
- In healthy volunteer studies in >140 patients, up to 500mg (SAD) and 300mg BID (MAD) was well tolerated; there were no DLTs and no MTD was reached

Next Steps

- Dose escalation across both groups ongoing
  - 400mg INCB00928 QD cohort
  - 200mg INCB00928 QD + ruxolitinib

INCB57643 (BET) + RUXOLITINIB

PETER LANGMUIR, MD

GVP, ONCOLOGY TARGETED THERAPEUTICS

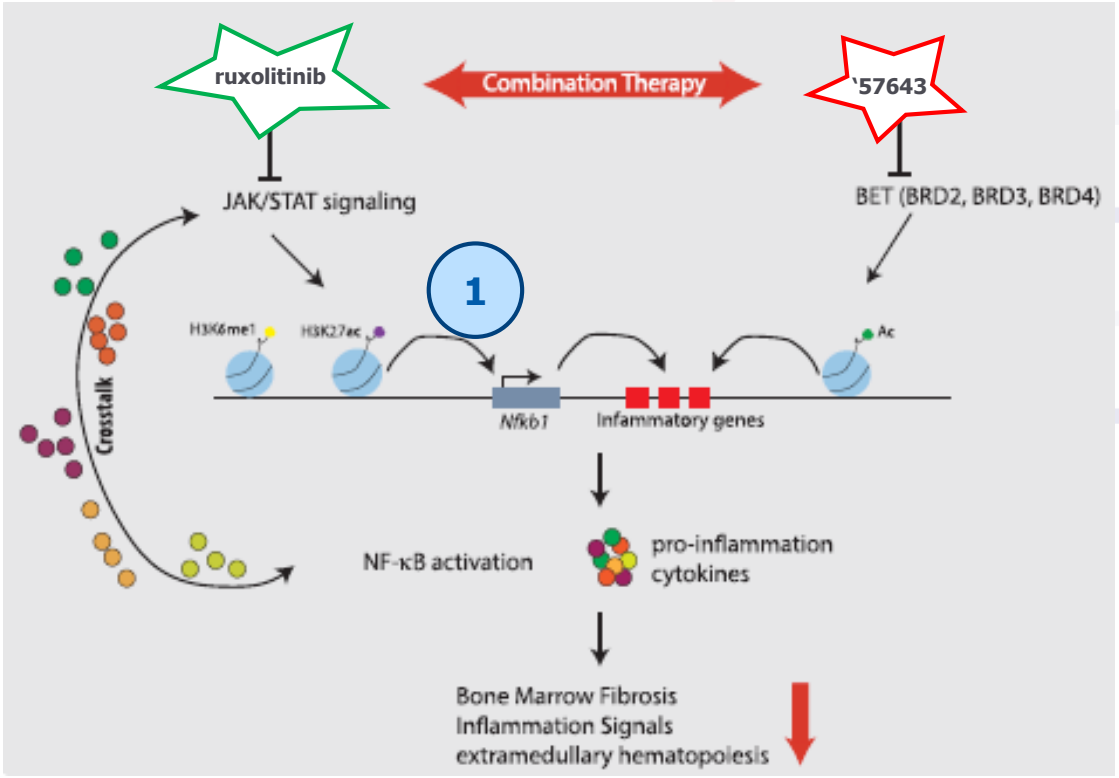
Rationale to combine ruxolitinib and BET/BRD inhibitor in MF

BET proteins regulate cell growth, survival and inflammation as well as NFκB activity

- NFκB implicated in regulating MPN-associated inflammation[1]
- Aberrant JAK2 signaling in MF leads to increased NFκB signaling[2,3]
- BET inhibitors reduced NFκB-induced inflammation and bone marrow fibrosis in MPN preclinical models[2,3]

Combined BET and JAK inhibition (in an MF mouse model)[2,3]:

- Reduced cytokine production
- Decreased inflammation and disease burden
- Eliminated bone marrow fibrosis



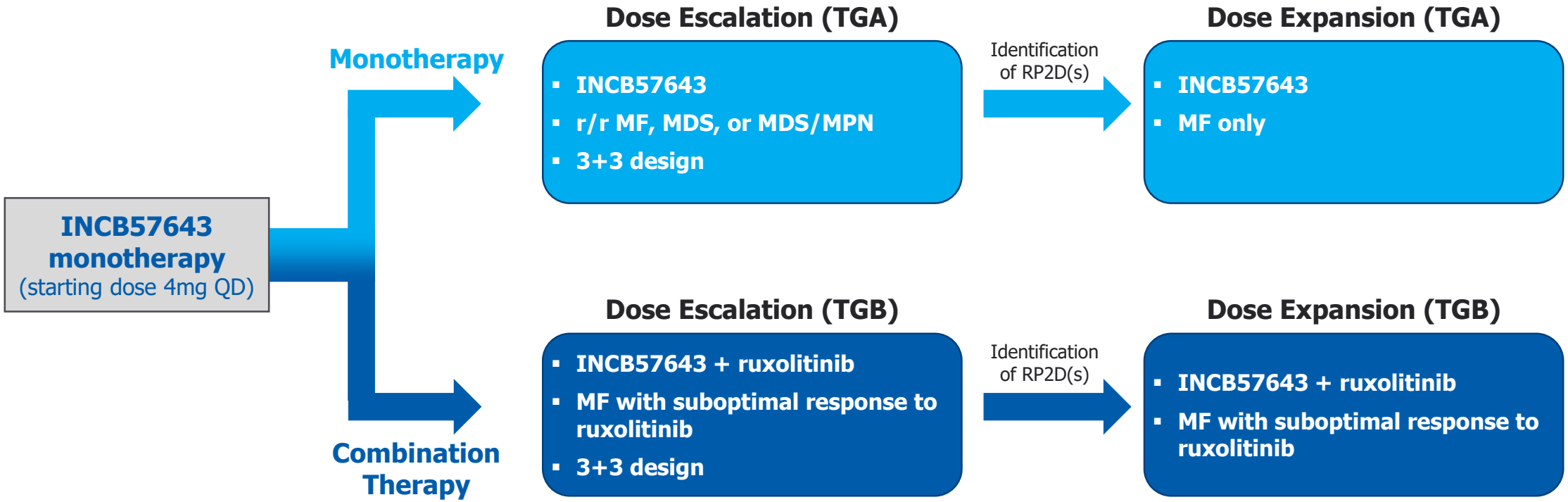
Adapted from Kleppe et al, 2018.

BET= bromodomain and extraterminal domain; BRD4= bromodomain-containing protein 4; $NF_{\kappa}B$ = nuclear factor kappa light chain enhancer of activated B cells

1. Belkina AC, et al. Nat Rev Cancer. 2012;12:465-477. 2. Ceribelli, et al. 2014. 3. Kleppe M, et al. Cancer Cell. 2018;33:29-43.e7.

INCB57643 (BET) ± ruxolitinib phase 1: Study design

- **Primary endpoint:** Safety and tolerability
- **Key secondary endpoints:** Spleen volume and length, overall response rate and symptom response



Adapted from Watts, et al., ASH 2022.
MDS = myelodysplastic syndromes; MF = myelofibrosis; MPN = myeloproliferative neoplasm; qd = once daily; r/r = relapsed or refractory; RP2D = recommended phase 2 dose; TGA = treatment group A; TGB = treatment group B

INCB57643 (BET) ± ruxolitinib phase 1: Baseline characteristics

- Advanced MF patients
- Heavily pre-treated MF patients; failed prior therapies
- Majority of patients previously on ruxolitinib
  - No washout required

Patient Demographics and Baseline Characteristics

Parameter	INCB057643 Treatment Group		
	4 mg (n=6)	8 mg (n=4)	Total (N=10)
Median (range) age, y	67.5 (59–77)	68.5 (65–79)	68.0 (59–79)
Male, n (%)	4 (66.7)	3 (75.0)	7 (70.0)
White	6 (100.0)	3 (75.0)	9 (90.0)
ECOG PS, n (%)			
0	1 (16.7)	0	1 (10.0)
1	5 (83.3)	4 (100.0)	9 (90.0)
Malignancy type, n (%)			
Primary MF	2 (33.3)	1 (25.0)	3 (30.0)
DIPSS Int-2	2 (33.3)	1 (25.0)	3 (30.0)
Post–PV-MF	2 (33.3)	0	2 (20.0)
DIPSS Int-2	2 (33.3)	0	2 (20.0)
Post–ET-MF	0	2 (50.0)	2 (20.0)
DIPSS Int-1	0	1 (25.0)	1 (10.0)
DIPSS Int-2	0	1 (25.0)	1 10.0)
Unclassifiable MDS/MPN overlap syndrome	1 (16.7)	1 (25.0)	2 (20.0)
CMML	1 (16.7)	0	1 (10.0)
RBC transfusion dependent	2 (33.3)	0	2 (20.0)
Prior treatment			
Ruxolitinib	4 (66.7)	3 (75.0)	7 (70.0)
Radiotherapy	1 (16.7)	1 (25.0)	2 (20.0)
Stem cell transplant	0	0	0
Mean (SD) spleen length below left costal margin, cm*	7.0 (3.6)	15.7 (0.6)	11.3 (5.3)

Adapted from Watts, et al., ASH 2022.

CMML, chronic myelomonocytic leukemia; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; ET, essential thrombocythemia; Int, intermediate; MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV-MF, polycythemia vera myelofibrosis; RBC, red blood cell.

* Among evaluable patients with MF: 4 mg cohort, n=3; 8 mg cohort, n=3.

INCB57643 (BET) monotherapy demonstrates signs of efficacy

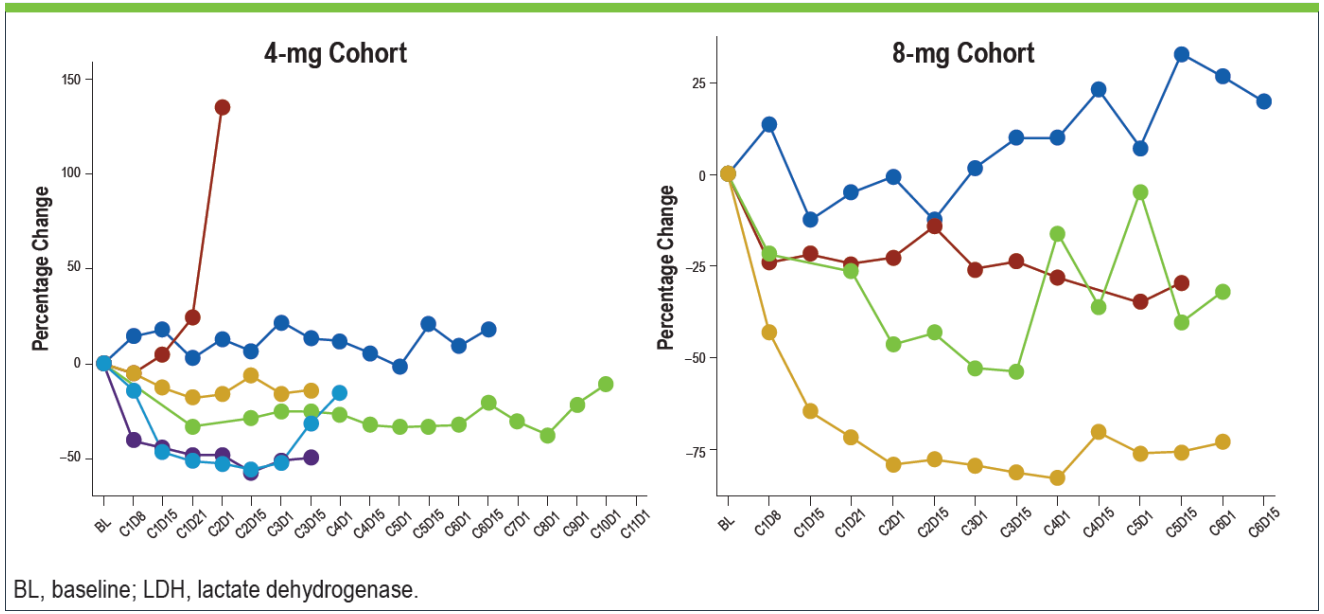
10 patients evaluated in part 1

- 4mg cohort (n=6), 1 remains on treatment
- 8mg cohort (n=4), 4 remain on treatment

Efficacy

- INCB57643 8mg QD reduced LDH, a general marker for inflammation
- Reductions in spleen length and volume from baseline was observed

Percentage Change from Baseline in LDH Levels in Individual Patients



BL, baseline; LDH, lactate dehydrogenase.

Best Percentage Change from Baseline in Spleen Volume and Length

Patient	Disease	Dose cohort	Spleen volume change,* %	Spleen length change,* %
1	PMF	4 mg	+53.3	+50.0
2	PMF	4 mg	NA	+133.3
3	Post–PV-MF	4 mg	+21.6	−10.0
4	PMF	8 mg	−29.0	−100
5	Post–ET-MF	8 mg	−5.5	0
6	Post–ET-MF	8 mg	NA	−25.0

Adapted from Watts, et al., ASH 2022.
ET = essential thrombocythemia; MF = myelofibrosis; NA = not available; PMF = primary myelofibrosis; PV = polycythemia vera. * Negative value indicates reduction in spleen size.

INCB57643 (BET) monotherapy was well tolerated in dose escalation

Safety of INCB57643 monotherapy (n=10 in part 1)

- No dose-limiting toxicities observed
- Thrombocytopenia and nausea were the only TEAEs that occurred in >2 patients in total population

Most common TEAEs, n (%)	INCB057643 Treatment Group					
	4 mg (n=6)		8 mg (n=4)		Total (N=10)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Thrombocytopenia*	3 (50.0)	1 (16.7)	1 (25.0)	1 (25.0)	4 (40.0)	2 (20.0)
Nausea	1 (16.7)	0	2 (50.0)	0	3 (30.0)	0
Anemia	2 (33.3)	2 (33.3)	0	0	2 (20.0)	2 (20.0)
Hyperuricemia	2 (33.3)	0	0	0	2 (20.0)	0
Hypokalemia	2 (33.3)	2 (33.3)	0	0	2 (20.0)	2 (20.0)

Adapted from Watts, et al., ASH 2022.
* Two of the 4 patients had moderate thrombocytopenia at baseline.

INCB57643 (BET) ± ruxolitinib: Conclusions

- INCB57643 8mg QD reduced LDH
- Reductions in spleen length and volume from baseline was observed with INCB57643 8mg QD
- INCB57643 monotherapy was generally well tolerated at doses of 4 and 8mg QD

Next Steps

- Enrollment is ongoing for:
  - 4mg INCB57643 + ruxolitinib in patients with MF and suboptimal response to ruxolitinib
  - 12mg INCB57643 monotherapy in patients with MF, MDS or MDS/MPN

MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasm.

INCA33989: MUTANT CALR ANTAGONIST ANTIBODY

PATRICK MAYES, PHD

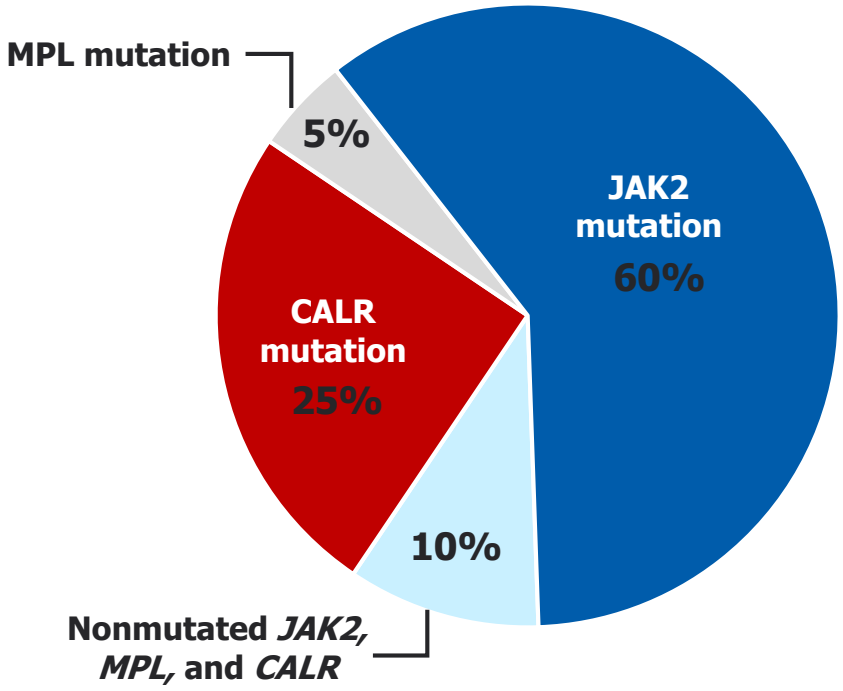
VP, BIOTHERAPEUTICS RESEARCH

Incyte | SOLVE ON.

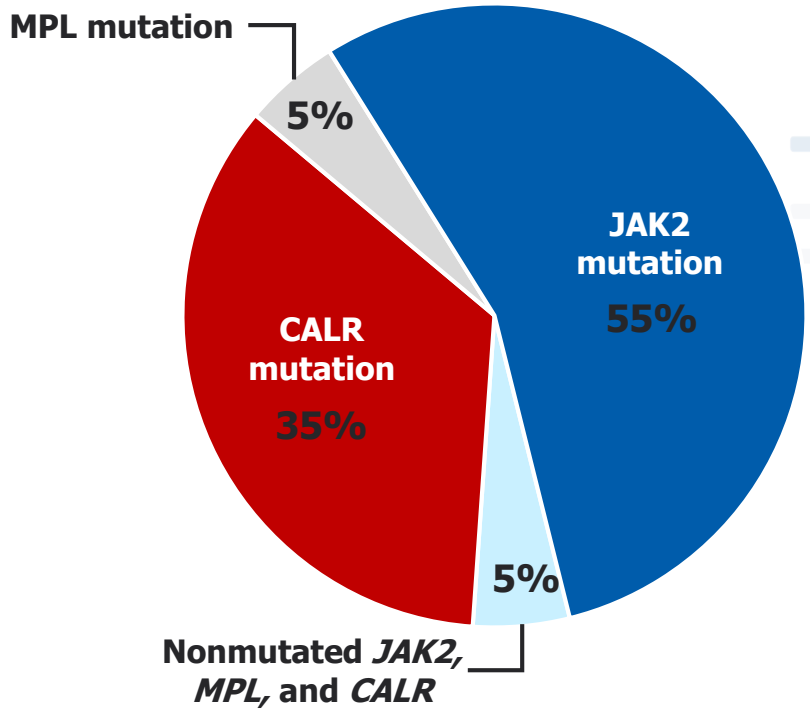
CALR Mutations are present in 25-35% of ET and MF patients

Distribution of *JAK2*, *MPL*, and *CALR* mutations in Philadelphia Chromosome-negative myeloproliferative neoplasms

Essential Thrombocythemia (N=311)



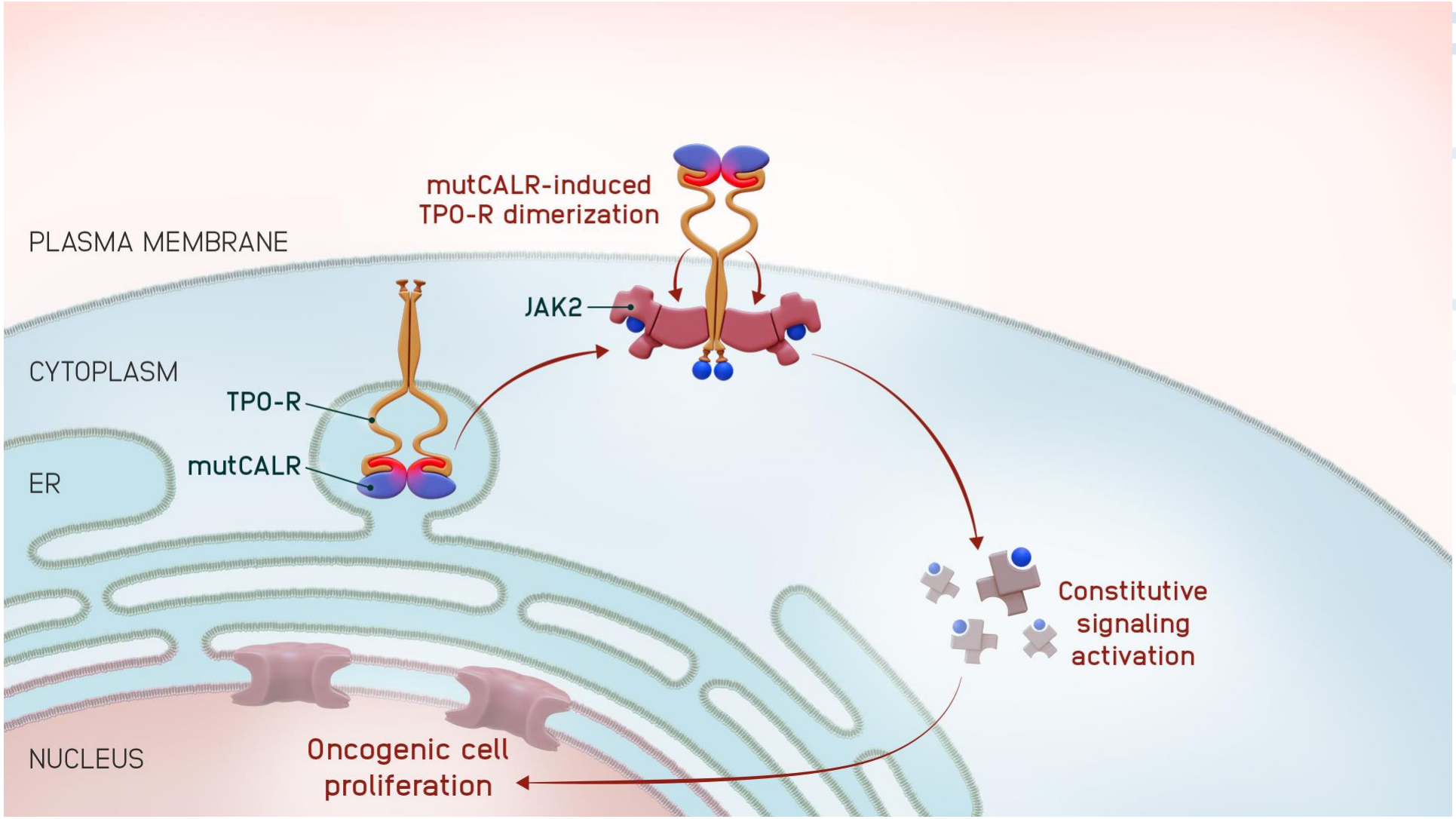
Primary Myelofibrosis (N=203)



CALR mutations are mutually exclusive with JAK2 or MPL mutations

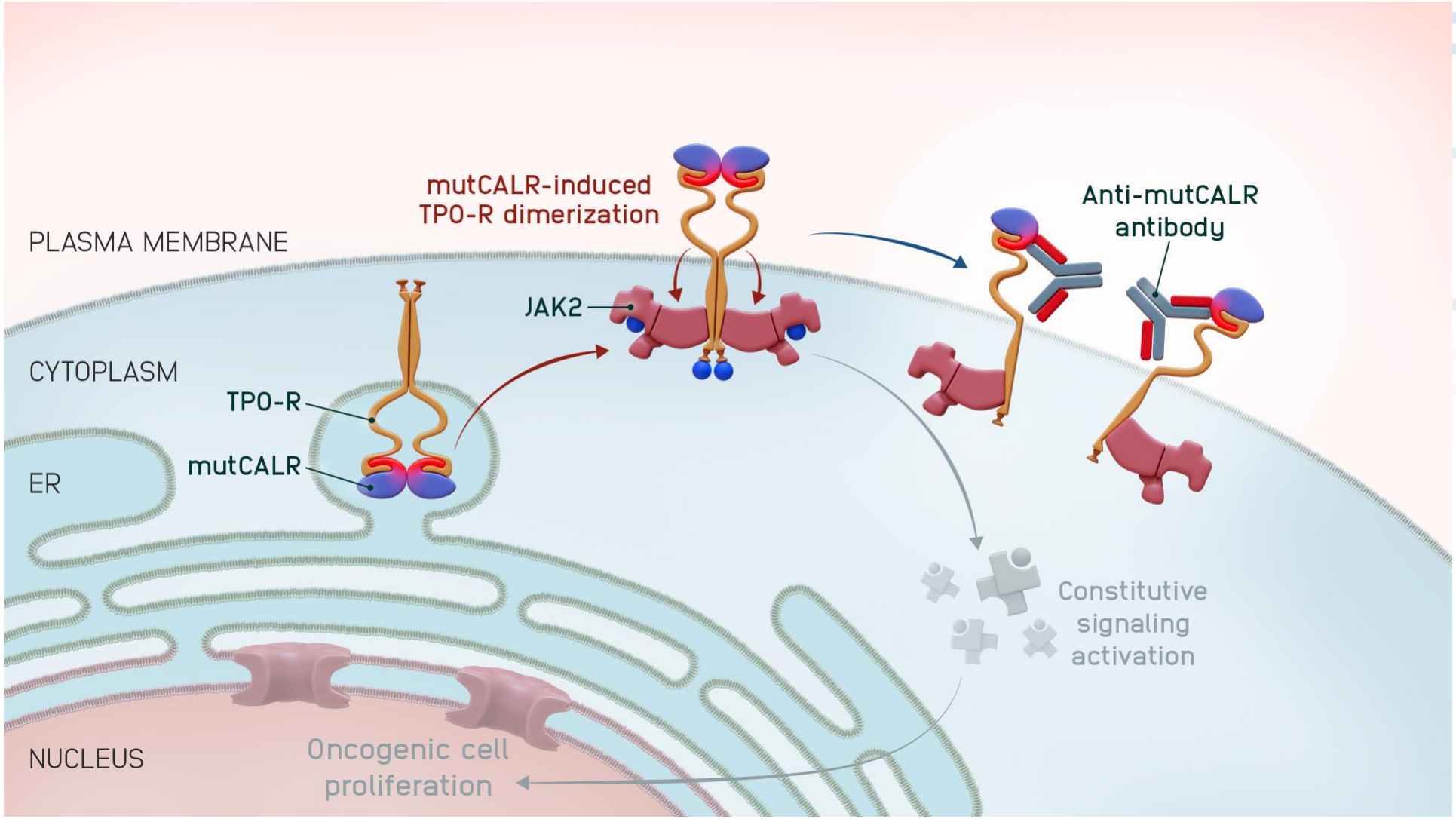
Adapted from Klampfl T. et al. N. Engl J Med. 2013 369:2379-2390

Mutant calreticulin (mutCALR) induces oncogenic cell proliferation



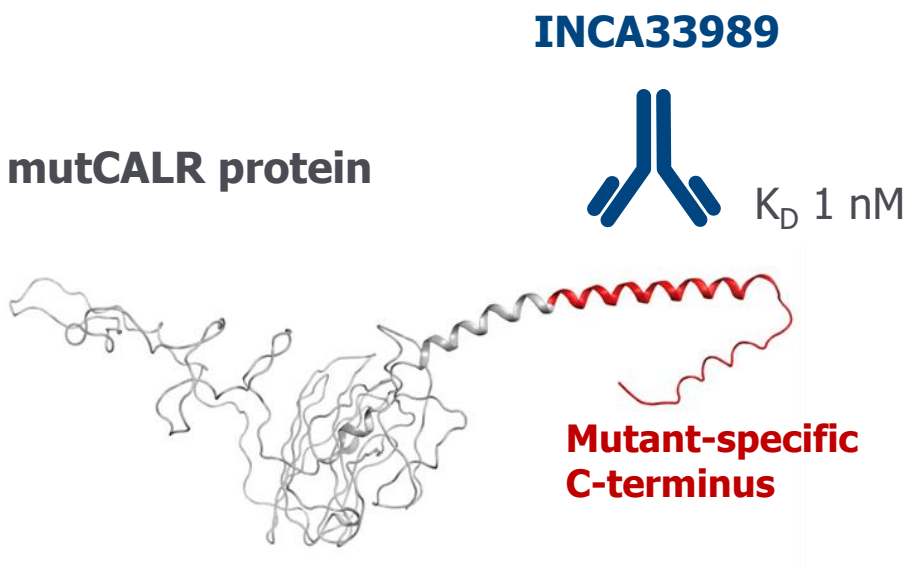
Adapted from Reis, et.al, ASH 2022.

Anti-mutCALR antibody selectivity inhibits oncogenic cell proliferation



Adapted from Reis, et.al, ASH 2022.

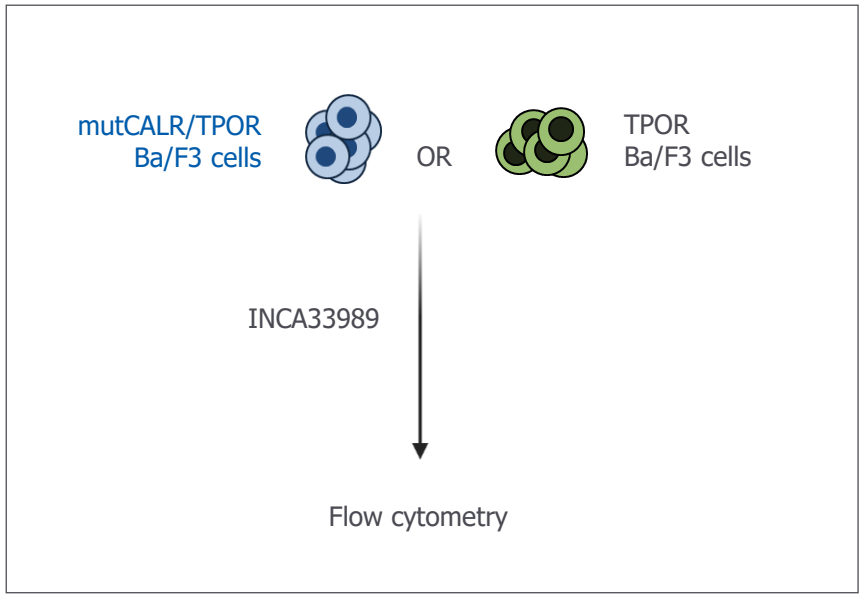
INCA33989 is a mutCALR-specific monoclonal antibody

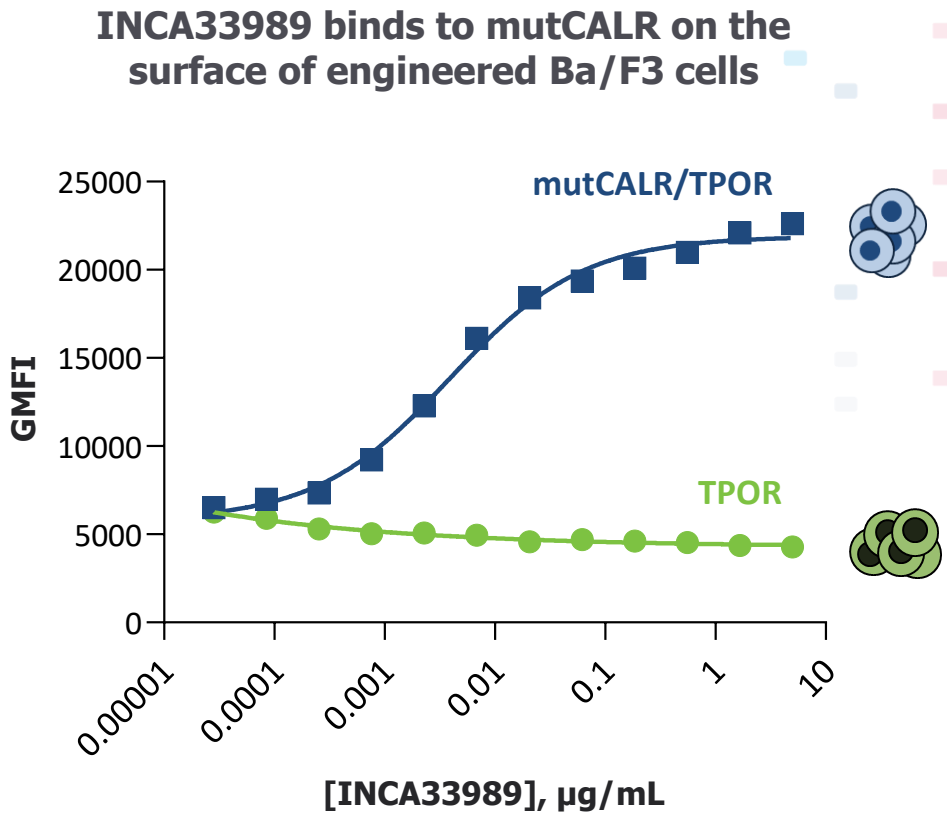


- Fully human Fc-silent IgG1
- Selective binding to mutCALR
- Antagonizes mutCALR-induced signaling and oncogenic function

Structure generated with RaptorX (Toyota Technological Institute at Chicago, IL, USA); IgG, immunoglobulin G; Fc, fragment crystallizable; KD, equilibrium dissociation constant.

INCA33989 selectively binds to mutCALR on engineered Ba/F3 cells

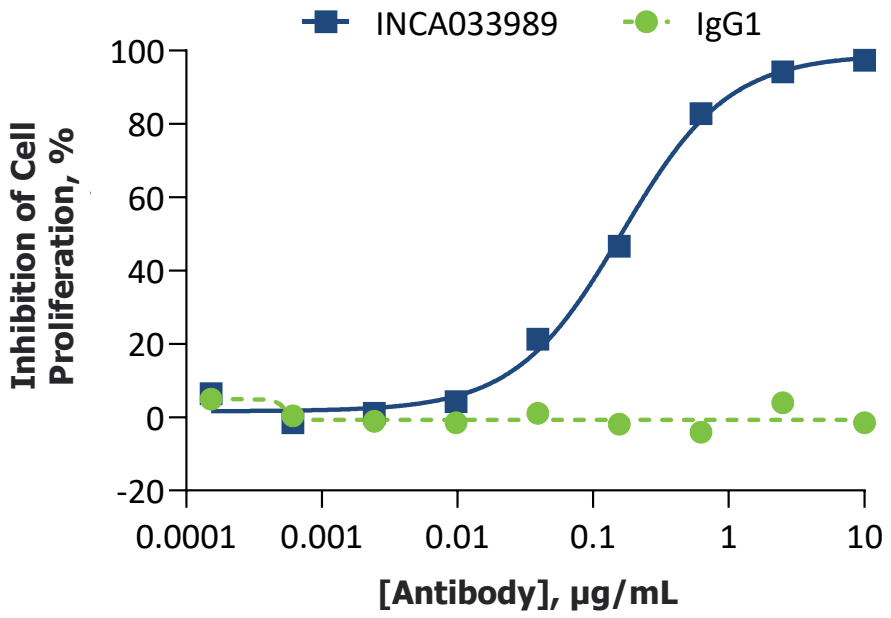




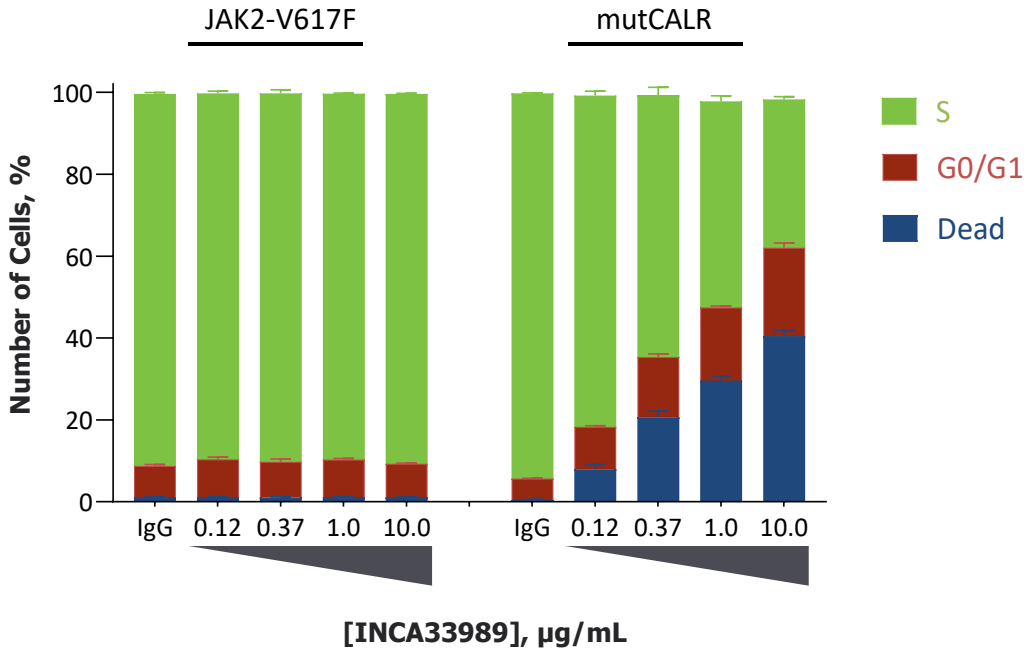
GMFI, geometric mean fluorescence intensity

INCA33989 selectively inhibits cell proliferation and induces death of mutCALR+ cells

INCA33989 inhibits mutCALR-dependent proliferation of Ba/F3 cells

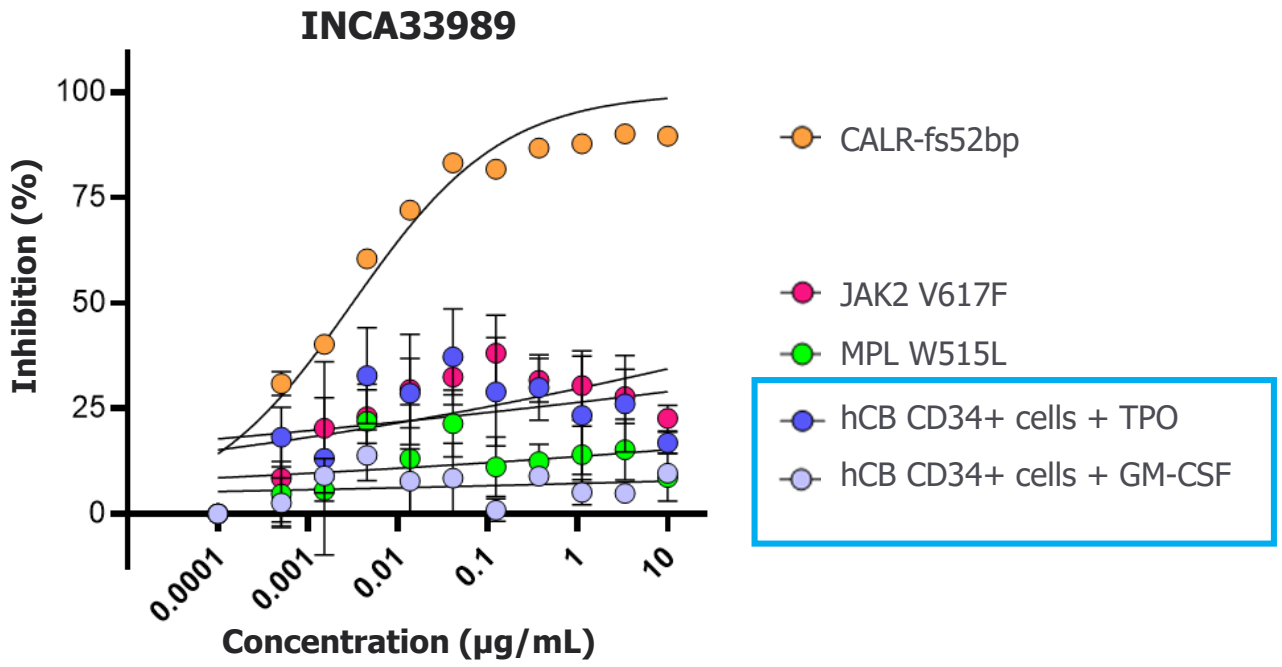


INCA33989 selectively induces death of mutCALR+ Ba/F3 cells



Adapted from Reis, et.al, ASH 2022.

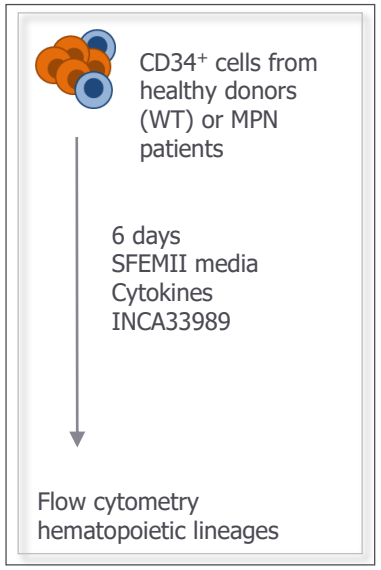
INCA33989 selectively inhibits JAK/STAT signaling in CALR mutant patient cells

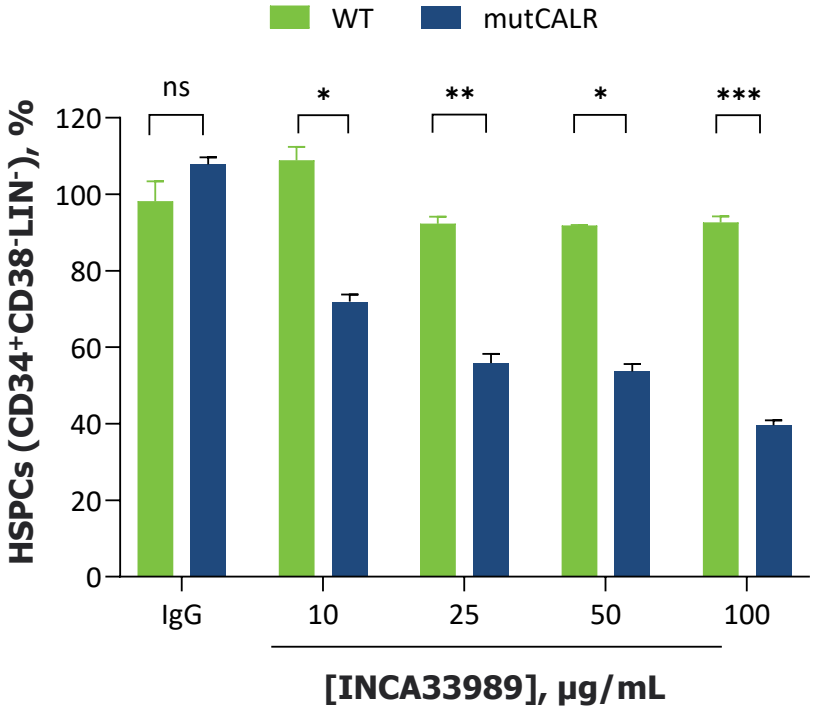


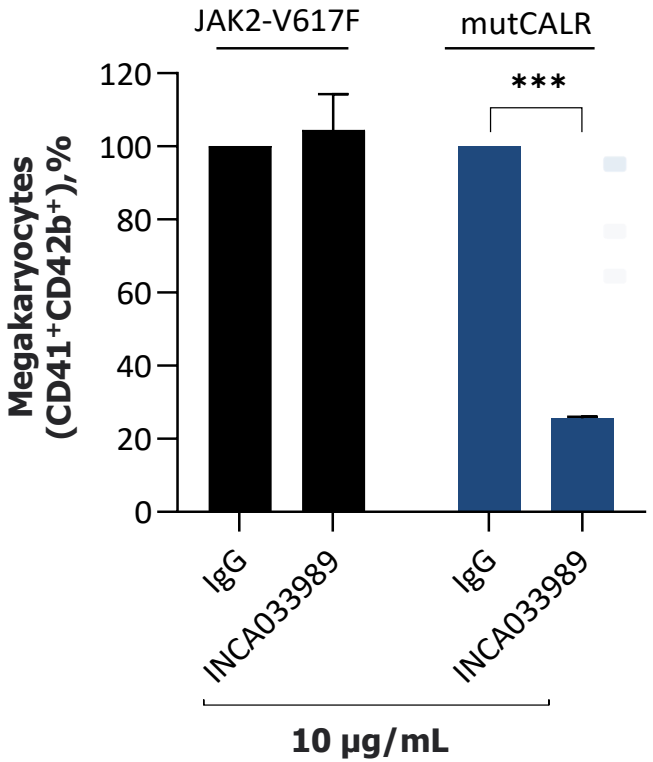
INCA33989 avoids inhibition of hCB CD34+ cells

Data on file, Incyte.
CD34+ cells isolated from PBMCs and expanded in vitro

INCA33989 selectively inhibits the proliferation of mutCALR+ HSPCs

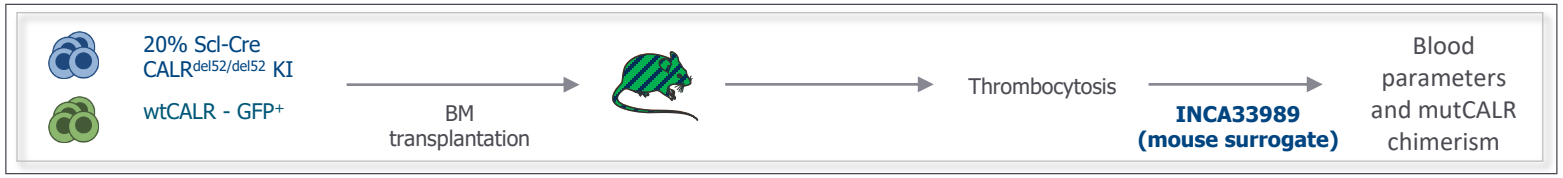


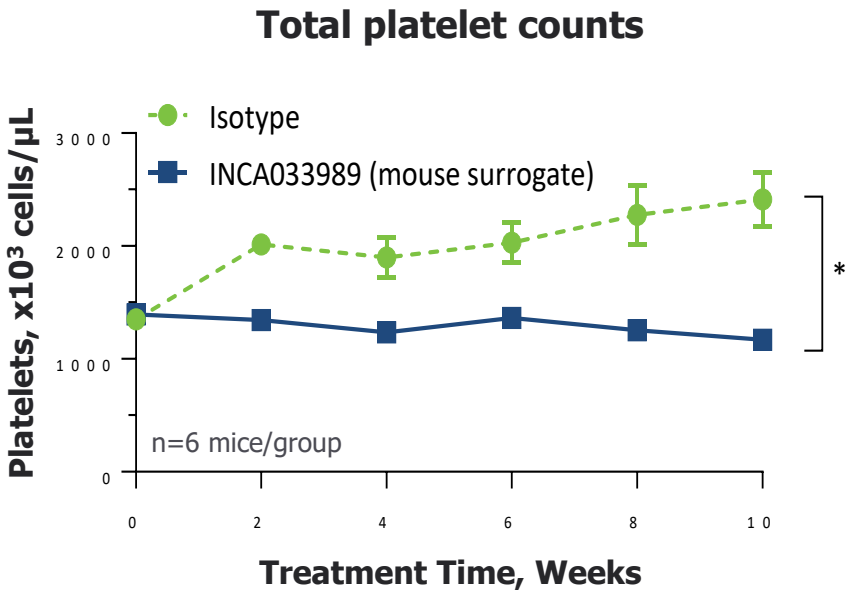


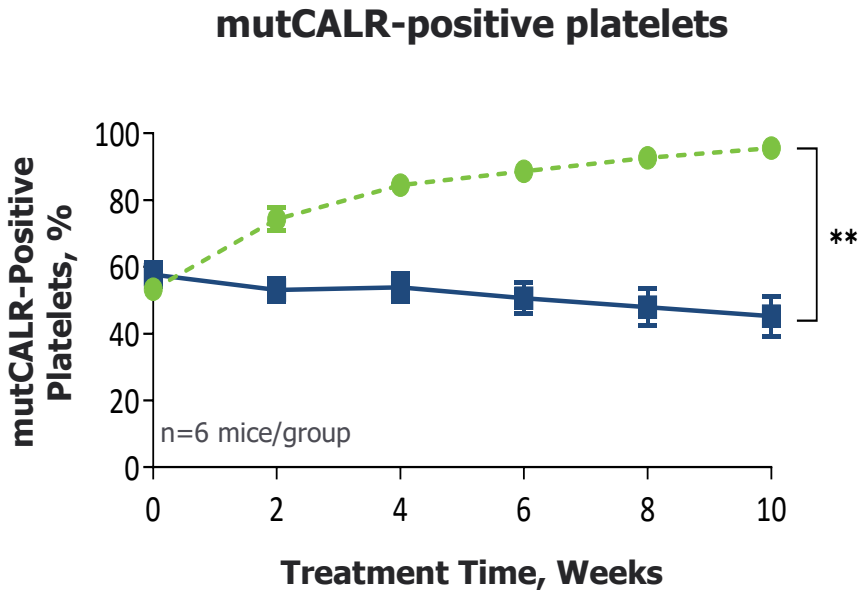


Adapted from Reis, et.al, ASH 2022.
*P<0.01; **P<0.001; ***P<0.0001.
HSPC, hematopoietic stem progenitor cells; ns, not significant.

INCA33989 surrogate restores hematologic and molecular responses in a murine model of ET



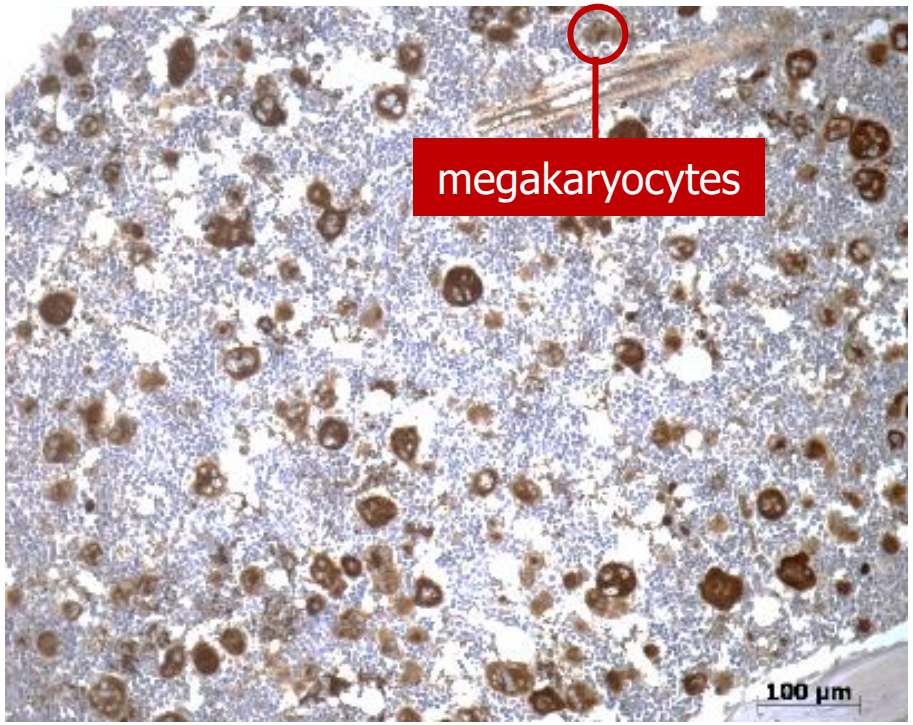




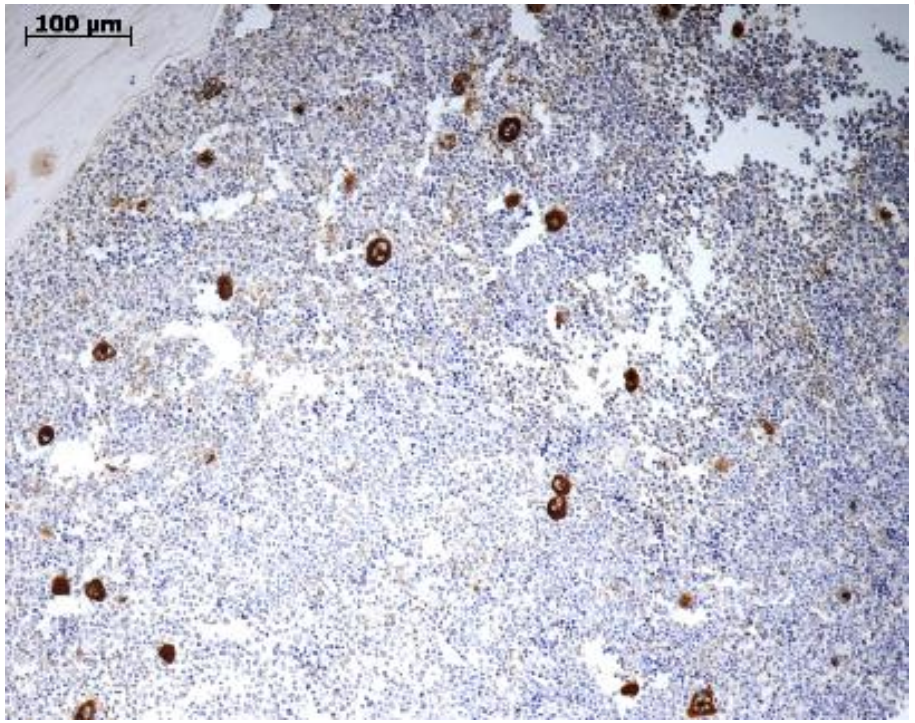
Adapted from Reis, et.al, ASH 2022.
*P<0.001; **P<0.0001.
BM, bone marrow; ET, essential thrombocythemia.

INCA33989 surrogate treatment re-establishes normal megakaryopoiesis

Isotype



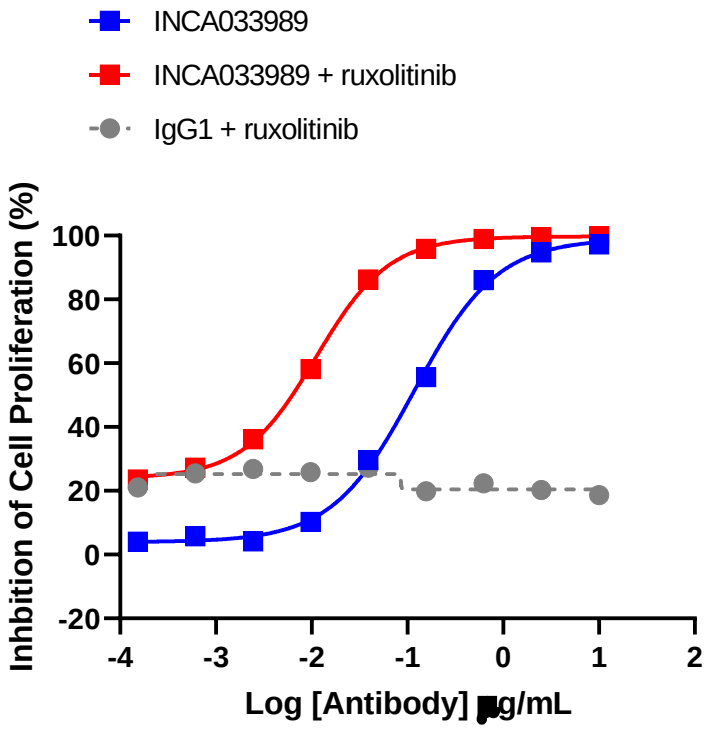
INCA33989 (mouse surrogate)



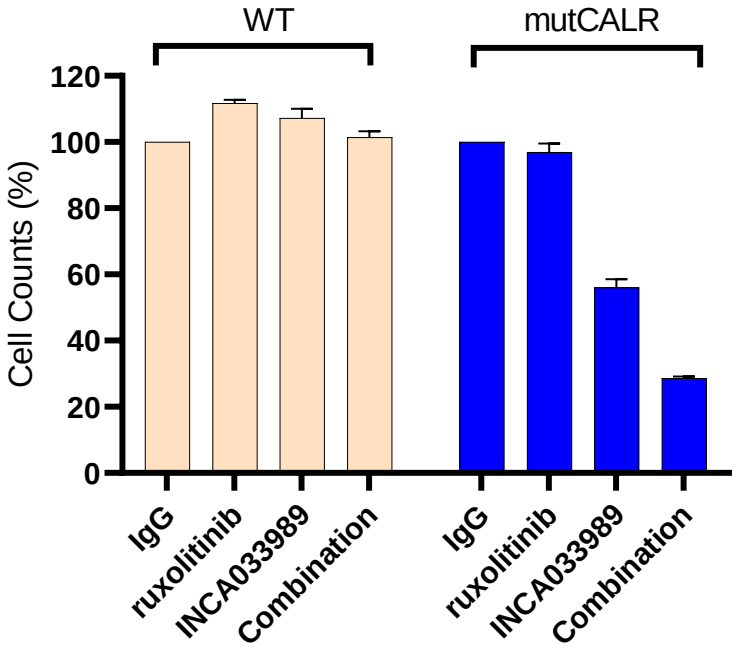
Adapted from Reis, et.al, ASH 2022.
Megakaryocytes stained with anti-von Willebrand factor antibody.

Combinatorial activity of INCA33989 and ruxolitinib

Combination of INCA33989 and ruxolitinib potentiates inhibition of cell proliferation



Functional synergy between INCA33989 and ruxolitinib is observed in megakaryocytes from patients with mutCALR



Data on file, Incyte.

Conclusion

- INCA33989 is a potent antagonist of mutant calreticulin function:
  - Selective inhibition of JAK/STAT signaling and proliferation of CALR-mutated stem progenitor cells
  - May mitigate clinical adverse events associated with broad inhibition of JAK/STAT in non-mutated cells
- Potential of INCA33989 as a single agent or in combination with ruxolitinib to alter the course of disease in ET and MF patients
- All in-life toxicology studies are complete with no adverse findings

Next Steps

- IND-enabling studies are ongoing
- Expect to initiate a phase 1 study in 2023

CLOSING COMMENTS

STEVEN STEIN, MD

CHIEF MEDICAL OFFICER, INCYTE

Incyte | SOLVE ON.

ASH 2022: Takeaways

Parsaclisib + ruxolitinib	**In MF patients with suboptimal response to ruxolitinib:** ▪ Substantial improvements in symptoms and spleen volume with addition of parsaclisib ▪ Combination was well tolerated with few drug-related AEs leading to discontinuation
INCB57643 (BET) + ruxolitinib	**In MF patients with suboptimal response or refractory to ruxolitinib:** ▪ Signs of clinical activity with monotherapy dose ▪ No DLTs or fatal TEAEs; dose escalation in monotherapy and combination ongoing
INCB00928 (ALK2) + ruxolitinib	**In MF patients who are transfusion dependent or have symptomatic anemia:** ▪ Hepcidin reduction and anemia responses achieved with monotherapy and combination ▪ Well tolerated; In prior studies*, up to 500mg QD (SAD) / 300mg BID (MAD) tested with no DLT
INCA33989 (mCALR)	**In preclinical MF or ET models with mutant CALR:** ▪ INCA33989 selectively binds to mutant CALR, induces cytostasis and death of mCALR+ cells ▪ Preclinical data supports development in MF and ET as monotherapy or in combination w/rux

*healthy volunteer studies; SAD = single-ascending dose; MAD = multiple ascending dose

LIMBER: Multiple opportunities to expand leadership in MPNs & GVHD

Myelofibrosis	Status	Upcoming Catalyst
QD ruxolitinib	NDA accepted	PDUFA: March 23, 2023
Parsaclisib + ruxolitinib	Suboptimal responder study ongoing	Top-line results end ’23
Parsaclisib + ruxolitinib	1L study ongoing	Top-line results end ‘24 / early ’25
ALK2 + ruxolitinib	Dose escalation ongoing	Combo data ’23
BET + ruxolitinib	Dose escalation ongoing	Combo data ’23
CK0804[1] + ruxolitinib	POC	
mCALR (INCA33989)	IND-enabling studies	Entering clinic in 2023
Novel Targets	Preclinical	

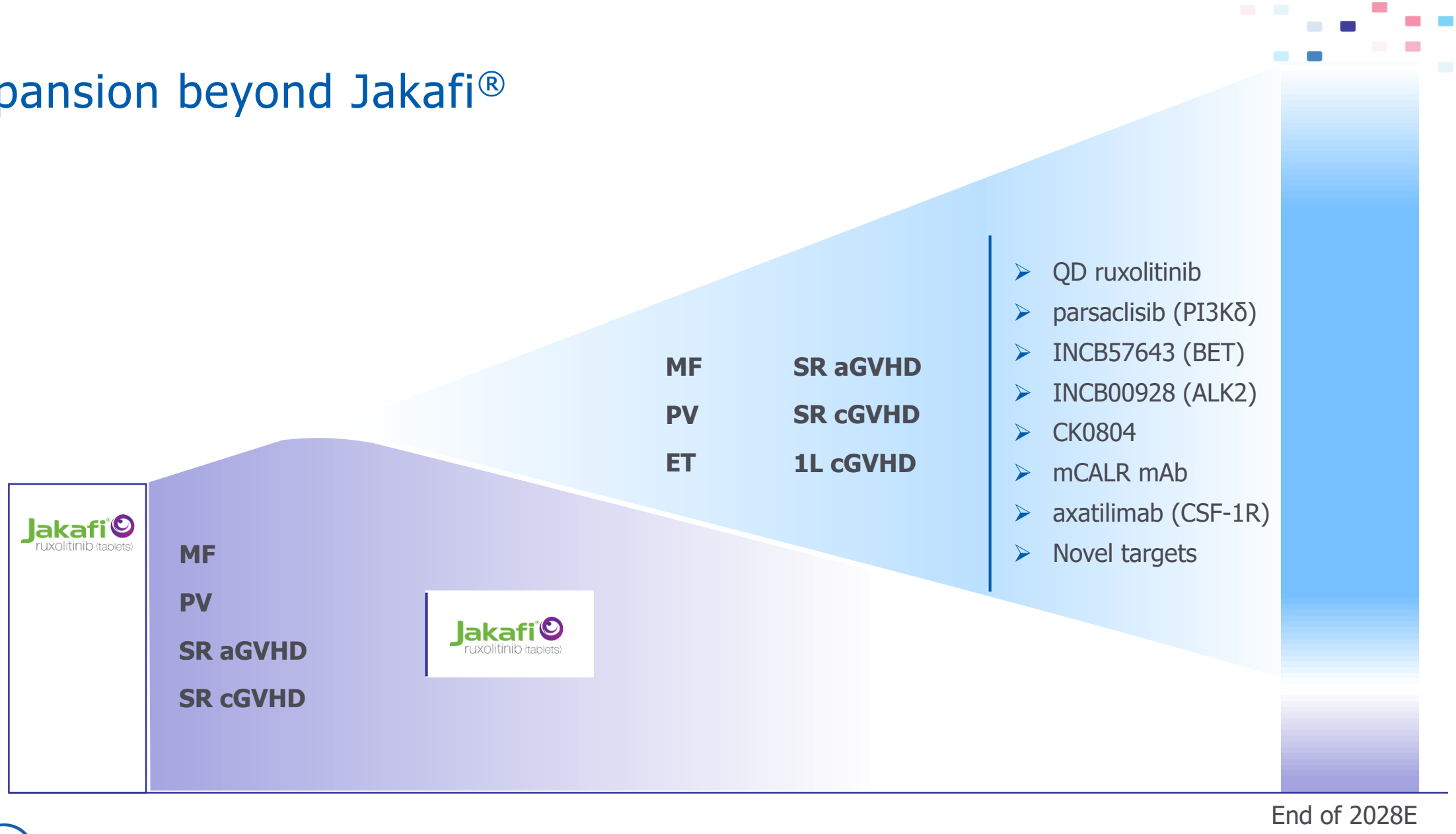
Polycythemia vera	Status	Upcoming Catalyst
Novel Targets	Preclinical	

Essential thrombocythemia	Status	Upcoming Catalyst
mCALR (INCA33989)	IND-enabling studies	
Novel Targets	Preclinical	

GVHD	Status	Upcoming Catalyst
axatilimab[2]	Pivotal Ph 2: AGAVE-201 (3L+ cGVHD)	Top-line results mid-’23
axatilimab[2]+ ruxolitinib	1L cGVHD trial initiating	

PoC = proof-of-concept; SN = steroid naïve
[1]Development of CK0804 plus ruxolitinib in collaboration with Cellenkos.
[2]Development of axatilimab in collaboration with Syndax Pharmaceuticals.

Expansion beyond Jakafi®



Jakafi (ruxolitinib) is approved by the FDA for treatment of adults with intermediate or high-risk myelofibrosis, for treatment of adults with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea and for the treatment of steroid-refractory acute and chronic GVHD in adult and pediatric patients 12 years and older.

Q&A

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