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**Myeloproliferative Neoplasms Including  
Chronic Myeloid Leukemia**

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Ann Arbor, MI

# Disclosures

*In compliance with ACCME policy, ASH requires disclosures to the session audience:*

## Speakers

Kristen Pettit, MD

## Disclosures

**Research Funding:** AbbVie; Blueprint Biomedicines; CTI Biopharma; Imago Biosciences; Kura Oncology; MacroGenics; PharmaEssentia; Protagonist

**Membership on a Board or Advisory Committee:** AbbVie; CTI Biopharma; Incyte; Sierra Oncology

**Discussion of off-label drug use:** Not applicable



# Learning Objectives

Upon participation in this activity, attendees will be able to:

- Describe current and upcoming treatment options for patients with MF, both cytopenic and non-cytopenic subtypes
- Understand the evolving treatment landscape for PV
- Recognize sub-optimal response in CML, and describe therapeutic options



# Case 1: Cytopenic Myelofibrosis

**79 yo M presents with fatigue, weight loss, and abdominal fullness**

- Exam: Splenomegaly (12 cm below costal margin)
- **CBC: WBC 2.3k (3% blasts), Hb 6.5 g/dL, platelets 41k**
- Bone marrow biopsy: 90% cellular marrow with myeloid expansion, dysplastic megakaryocytes in clusters, and MF-3 fibrosis with 5% myeloid blasts
- Cytogenetics: Normal Karyotype
- Myeloid NGS panel: JAK2 V617F+, ASXL1+

**Diagnosis: Primary Myelofibrosis, Cytopenic subtype**

Risk Stratification: DIPSS+ High Risk, MIPSS70+v2.0 Very High Risk



What is the best treatment option for this older patient patient with cytopenic, high-risk MF and symptomatic splenomegaly?

- A. Ruxolitinib 20 mg BID
- B. Fedratinib 400 mg daily
- C. Pacritinib 200 mg BID (if available)
- D. Allogeneic stem cell transplant
- E. Active observation

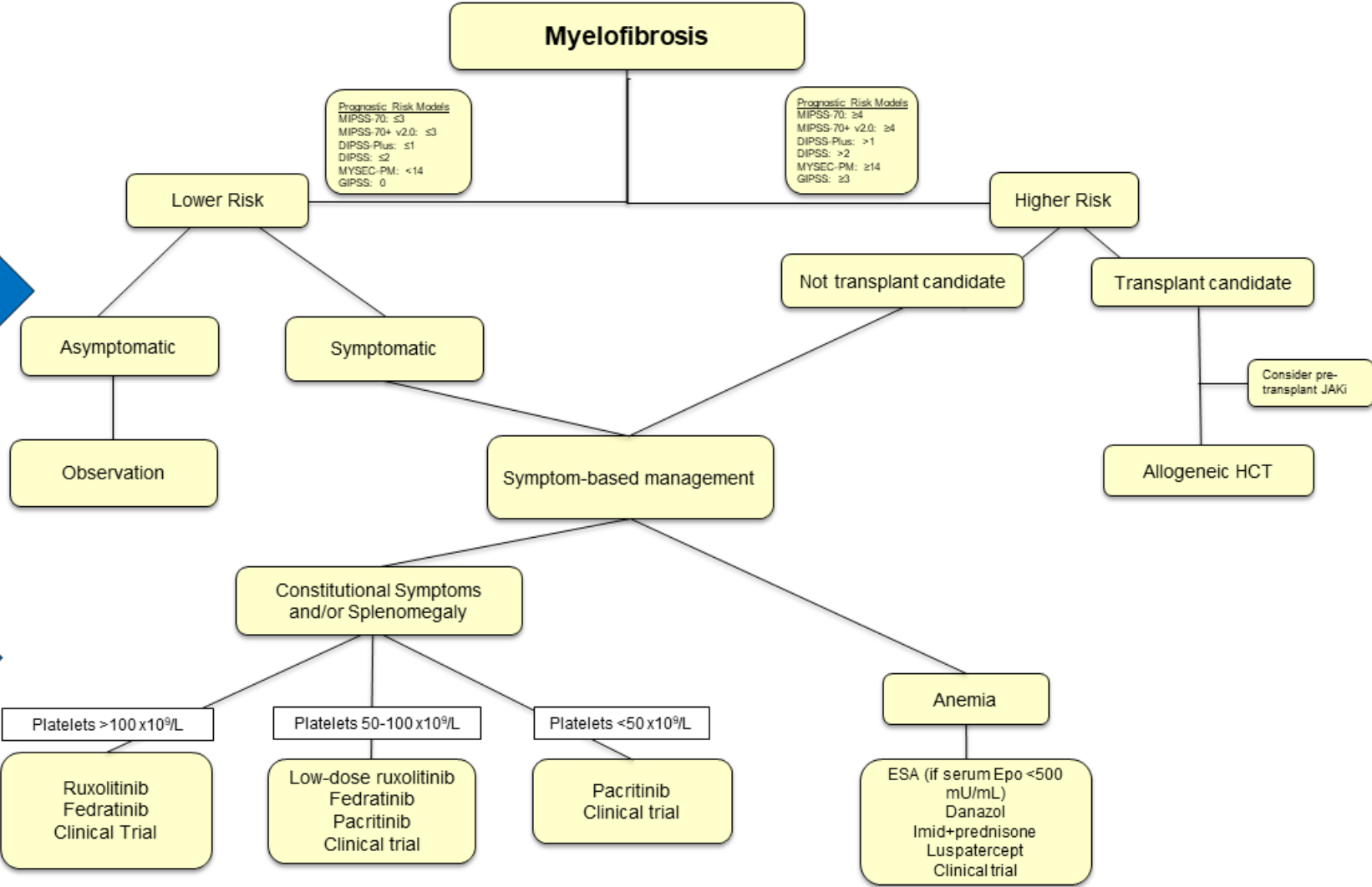


# Myelofibrosis Treatment Algorithm

1. Assess disease risk


2. Evaluate for symptoms and/or splenomegaly

3. Consider cytopenias



# Current JAK Inhibitor Landscape



JAKi	Ruxolitinib	Fedratinib	Pacritinib 
<b>Targets</b>	JAK1, JAK2	JAK2, JAK1 (less), FLT3, TYK2, many others	JAK2, IRAK1, FLT3, ACVR1
<b>Indication</b>	Intermed or high-risk MF with platelets $\geq 50k$	Intermed-2 or high-risk MF with platelets $\geq 50k$	Intermed or high-risk MF with <b>platelets <math>&lt; 50k</math></b>
<b>Clinical practice points</b>	Hematologic toxicities	Hematologic toxicities GI toxicities Monitor thiamine	Less cytopenia-inducing GI toxicities Monitor QTc Monitor for bleeding





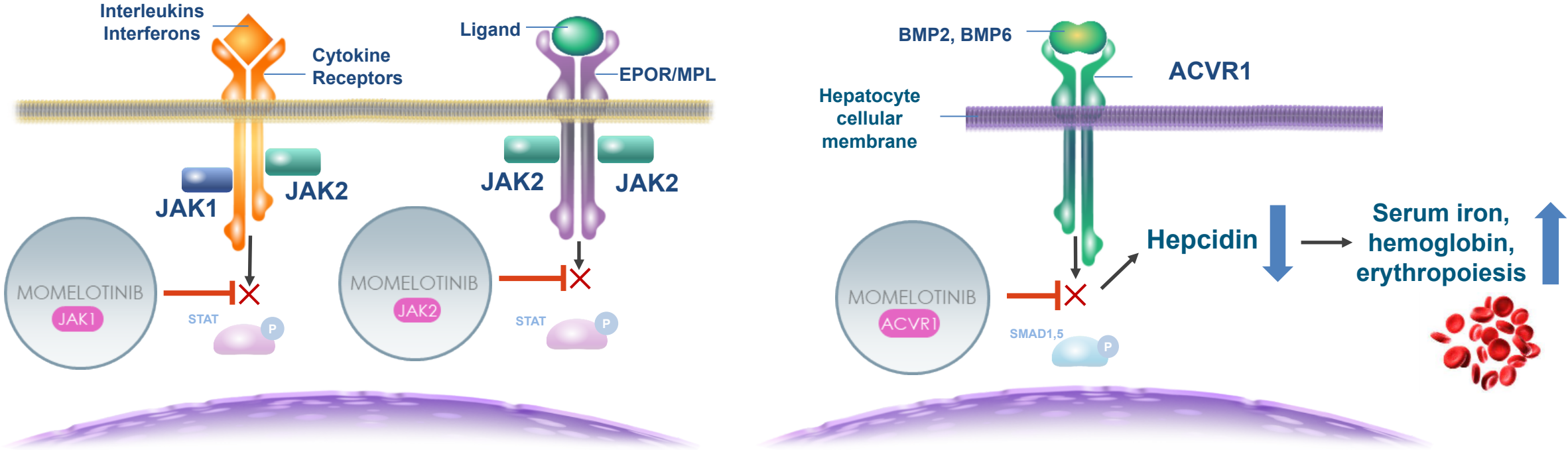
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## Updated Results from the Momentum Phase 3 Study of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic and Anemic Myelofibrosis (MF) Patients Previously Treated with a JAK Inhibitor

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# Momelotinib Inhibits JAK1, JAK2, and ACVR1 to Address MF Symptoms, Spleen, and Anemia

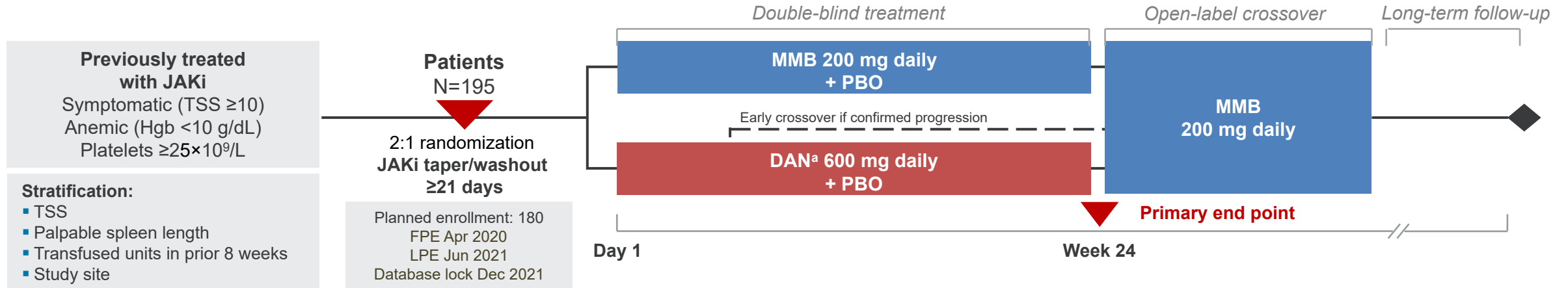


Dysregulated **JAK-STAT signaling** in MF drives overproduction of inflammatory cytokines, **bone marrow fibrosis, systemic symptoms**, and clonal proliferation resulting in extramedullary hematopoiesis and **splenomegaly**<sup>1,2</sup>

Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF<sup>3,4</sup>

ACVR1, activin A receptor type 1; BMP, bone morphogenetic protein; EPOR, erythropoietin receptor; JAK, Janus kinase; MF, myelofibrosis; MPL, myeloproliferative leukemia protein; SMAD1/5, mothers against decapentaplegic homolog 1/5; STAT, signal transducer and activator of transcription.  
 1. Chifolides HT, et al. *J Hematol Oncol.* 2022;15(1):7. 2. Verstovsek S, et al. *Future Oncol.* 2021;17(12):1449-1458. 3. Asshoff M, et al. *Blood.* 2017;129(13):1823-1830. 4. Oh ST, et al. *Blood Adv.* 2020;4(18):4282-4291.

# MOMENTUM Is an Ongoing Phase 3 Study of Mometotinib Versus DAN in Symptomatic, Anemic, JAKi-Experienced Patients



# MOMENTUM Results

**MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met<sup>1,2</sup>**

	MFSAF TSS <sup>b</sup> response rate (primary end point)	TI response <sup>c</sup> rate	SRR <sup>d</sup> (35% reduction)
<b>MMB (N=130)</b>	32 (24.6%)	40 (30.8%)	30 (23.1%)
<b>DAN (N=65)</b>	6 (9.2%)	13 (20.0%)	2 (3.1%)
	<i>P</i> =.0095 (superior)	1-sided <i>P</i> =.0064 (noninferior)	<i>P</i> =.0006 (superior)



# TEAEs in $\geq 10\%$ of Patients During OL MMB Treatment with No New Safety Signals Detected

	MMB $\rightarrow$ MMB (n=93)		DAN $\rightarrow$ MMB (n=41)	
	% of patients			
Grade $\geq 3$ adverse events	49.5		46.3	
Serious adverse events	31.2		29.3	
	Any grade	Grade $\geq 3$	Any grade	Grade $\geq 3$
<b>Nonhematologic (preferred term)</b>				
Weight decreased	7.5	0	14.6	0
Diarrhea	14.0	1.1	12.2	0
Pyrexia	14.0	0	7.3	0
Hypertension	3.2	0	12.2	2.4
Asthenia	11.8	3.2	0	0
<b>Hematologic (preferred term)</b>				
Thrombocytopenia	14.0	8.6	17.1	14.6
Anemia	10.8	8.6	7.3	2.4
Neutropenia	5.4	5.4	4.9	0
<b>Other</b>				
COVID-19 (pneumonia)	10.8	5.4	0	0
Peripheral sensory neuropathy	2.2	0	2.4	0



DAN, danazol; MMB, momelotinib; OL, open-label; TEAE, treatment-emergent adverse event.





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# Pacritinib Is a Potent ACVR1 Inhibitor with Significant Anemia Benefit in Patients with Myelofibrosis

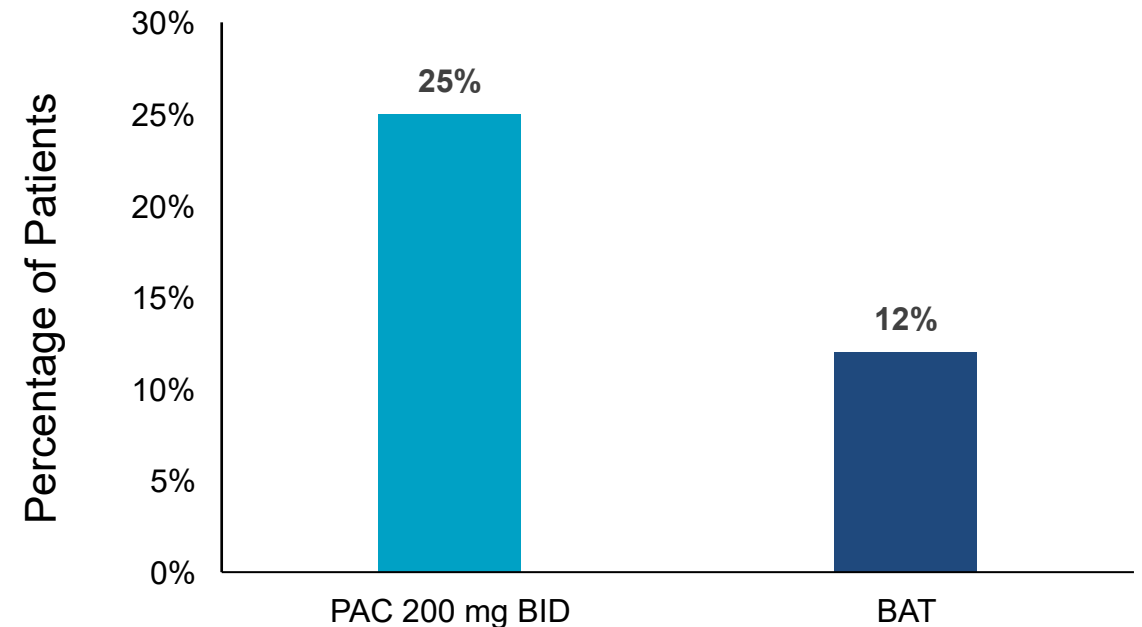
Stephen T. Oh,<sup>1</sup> Ruben A. Mesa,<sup>2</sup> Claire N. Harrison,<sup>3</sup> Prithviraj Bose,<sup>4</sup> Aaron T. Gerds,<sup>5</sup> Mark L. Heaney,<sup>6†</sup> Vikas Gupta,<sup>7</sup> Bart L. Scott,<sup>8</sup> Jean-Jacques Kiladjan,<sup>9</sup> Alessandro Lucchesi,<sup>10</sup> Tim Kong,<sup>1</sup> Sarah A. Buckley,<sup>11</sup> Shanthakumar Tyavanagimatt,<sup>11</sup> Karisse Roman-Torres,<sup>11</sup> John Mascarenhas,<sup>12</sup> Srdan Verstovsek<sup>4</sup>

<sup>1</sup>Washington University School of Medicine, St. Louis, MO; <sup>2</sup>UT Health San Antonio Cancer Center, San Antonio, TX; <sup>3</sup>Guy's and St Thomas' NHS Trust, London, United Kingdom; <sup>4</sup>The University of Texas MD Anderson Cancer Center, Houston, TX; <sup>5</sup>Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; <sup>6</sup>Columbia University Medical Center, New York, NY; <sup>7</sup>Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; <sup>8</sup>Fred Hutchinson Cancer Research Center, Seattle, WA; <sup>9</sup>Hôpital Saint-Louis, Université de Paris, Paris, France; <sup>10</sup>IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola (FC), Italy; <sup>11</sup>CTI BioPharma, Seattle, WA; <sup>12</sup>Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

# Pacritinib in Cytopenic Myelofibrosis

- Approved in patients with MF who have a platelet count  $<50 \times 10^9/L$
- Able to be administered at the full approved dose (200 mg BID) regardless of cytopenias<sup>1-3</sup>
- Demonstrated hemoglobin improvement in randomized PERSIST-2 study<sup>2</sup>
- The mechanism behind / extent of anemia benefit has not been fully described

## Clinical Improvement in Hemoglobin<sup>2</sup> PERSIST-2, Week 24




**IWG criteria:** among patients with baseline hemoglobin  $<10$  g/dL, increase of  $\geq 2.0$  g/dL or RBC transfusion independence for  $\geq 8$  weeks

BAT=best available therapy; BID=twice daily; IWG= ; MF=myelofibrosis; RBC=red blood cell.

[1] Mesa R, et al. *Lancet Oncology*; 2017. [2] Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659. [3] Gerds A, et al. *Blood Advances*. 2020;4(22):5825-35.

# Pacritinib Is a Potent ACVR1 Inhibitor

- **Pacritinib is ~4x more potent** than momelotinib against ACVR1

	<b>+ Control</b> LDN 193189 <sup>a</sup>	<b>PAC</b> C <sub>max</sub> 213 nM	<b>MMB</b> C <sub>max</sub> 168 nM	<b>FED</b> C <sub>max</sub> 275 nM	<b>RUX</b> C <sub>max</sub> 47 nM	<b>Legend</b>  Higher potency Lower potency
<b>Replicate 1</b> ACVR1 IC <sub>50</sub> (nM)	20.4	22.6	70.2	312.0	>1000	
<b>Replicate 2</b> ACVR1 IC <sub>50</sub> (nM)	32.4	10.8	34.9	235.0	>1000	
<b>Mean</b> ACVR1 IC <sub>50</sub> (nM)	26.4	16.7	52.6	273.5	>1000	
<b>Potency<sup>b</sup></b> (C <sub>max</sub> :IC <sub>50</sub> )	N/A	12.7	3.2	1.0	<0.01	

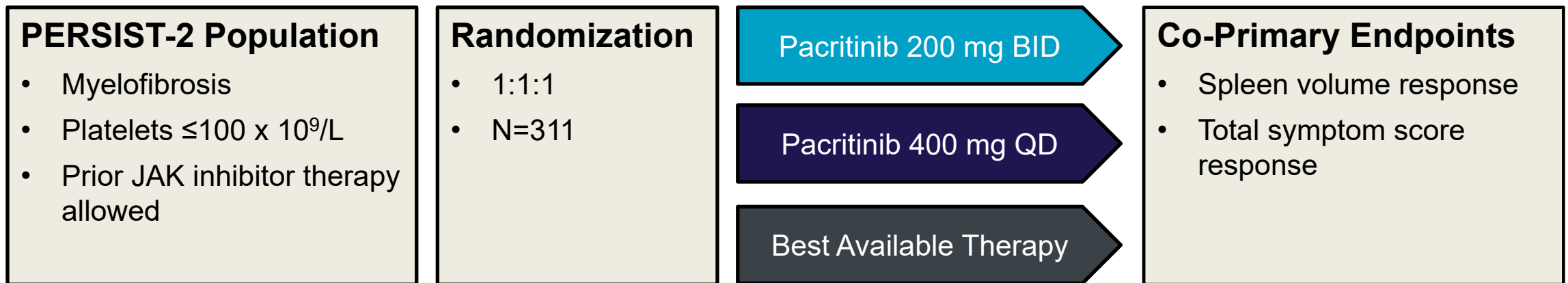
<sup>a</sup>LDN 193189 is an ACVR1 inhibitor.

<sup>b</sup>C<sub>max</sub> is the maximum unbound plasma concentration at the clinical recommended dose in humans.

ACVR1= Activin A receptor type 1; FED=fedratinib; IC<sub>50</sub>=half maximal inhibitory concentration; MOM=momelotinib; PAC=pacritinib; RUX=ruxolitinib.

# Methods: Analysis of Transfusion Independence

- Evaluated pacritinib 200 mg BID (approved dose) and best available therapy (BAT) on PERSIST-2 study<sup>1</sup>



**What percentage became TI on study through week 24?**

- TI (Gale criteria): no RBC transfusion over 12 weeks

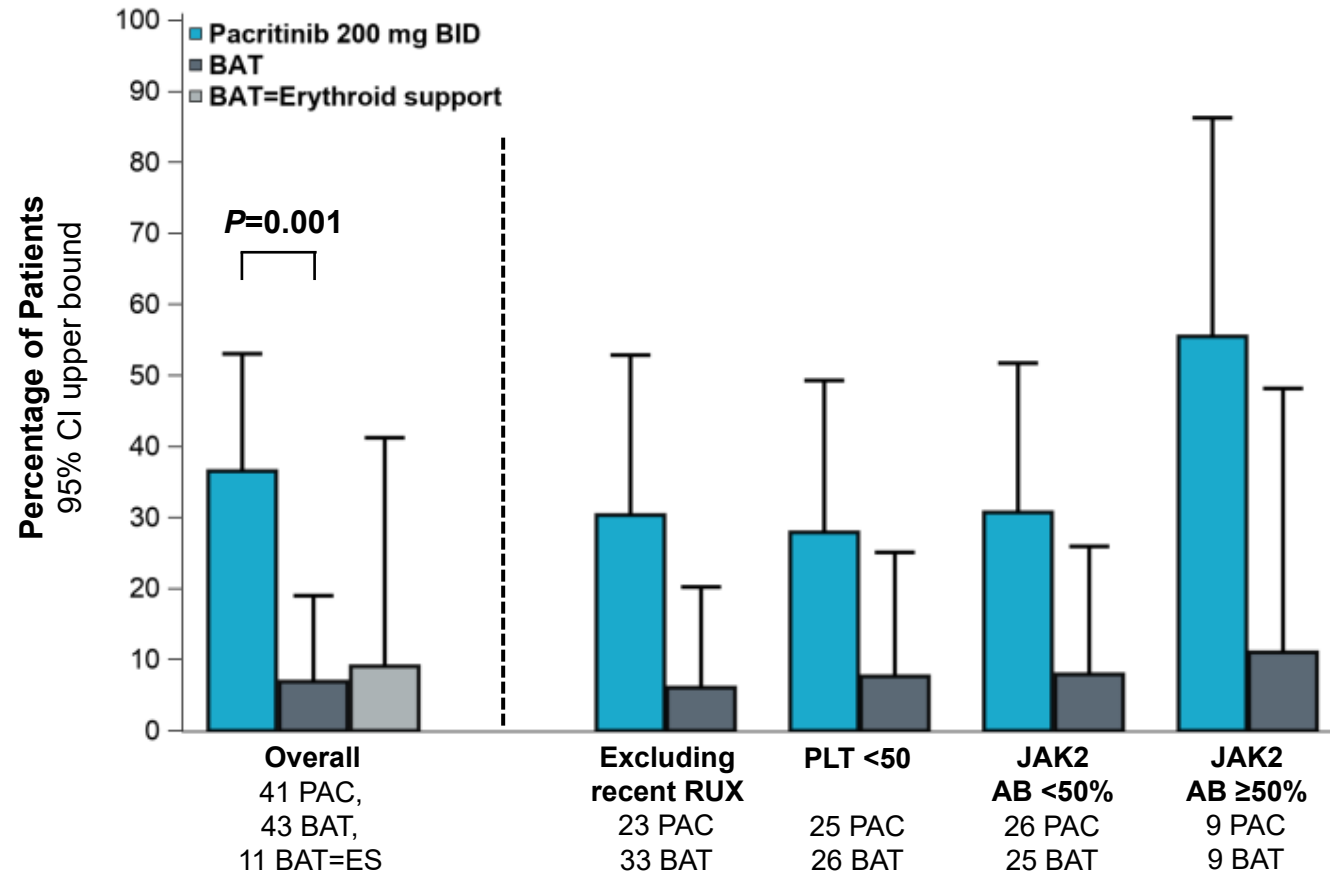
# More Pacritinib Patients Achieved TI (Gale)

## TI Conversion Rate

Pacritinib N=41	BAT N=43	P-value
37%	7%	0.001

- TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT
  - Erythroid support agents were prohibited on the pacritinib arm

## Rate of TI (Gale criteria) through Week 24



AB=allele burden; BAT=best available therapy; ES=erythroid support; JAK=Janus associated kinase; PAC=pacritinib; PLT=platelets; recent RUX=no ruxolitinib in prior 30 days; TI=transfusion independence.

# Case 2: Newly Diagnosed Myelofibrosis

**76 yo M presents with fatigue, weight loss, and abdominal fullness**

- Exam: Splenomegaly (12 cm below costal margin)
- **CBC: WBC 9.5k (3% blasts), Hb 10.5 g/dL, platelets 181k**
- Bone marrow biopsy: 90% cellular marrow with myeloid expansion, dysplastic megakaryocytes in clusters, and MF-3 fibrosis with 5% myeloid blasts
- Cytogenetics: Normal Karyotype
- Myeloid NGS panel: JAK2 V617F+, ASXL1+

**Diagnosis: Primary Myelofibrosis**

Risk Stratification: DIPSS+ Intermediate-2 Risk, MIPSS70+v2.0 High Risk

What is the best frontline treatment for MF?

What upfront treatment options could be used for this patient with symptomatic (non-cytopenic) MF?

- A. Ruxolitinib
- B. Fedratinib
- C. Clinical trial of ruxolitinib + a novel agent
- D. All of the above

# Frontline Studies of Combination therapy for MF

- Ruxolitinib vs Ruxolitinib + Pelabresib (BET inhibitor)
- Ruxolitinib vs Ruxolitinib + Navitoclax (BCL2/BCLxL inhibitor)
- Ruxolitinib vs Ruxolitinib + Parsaclisib (PI3K inhibitor)



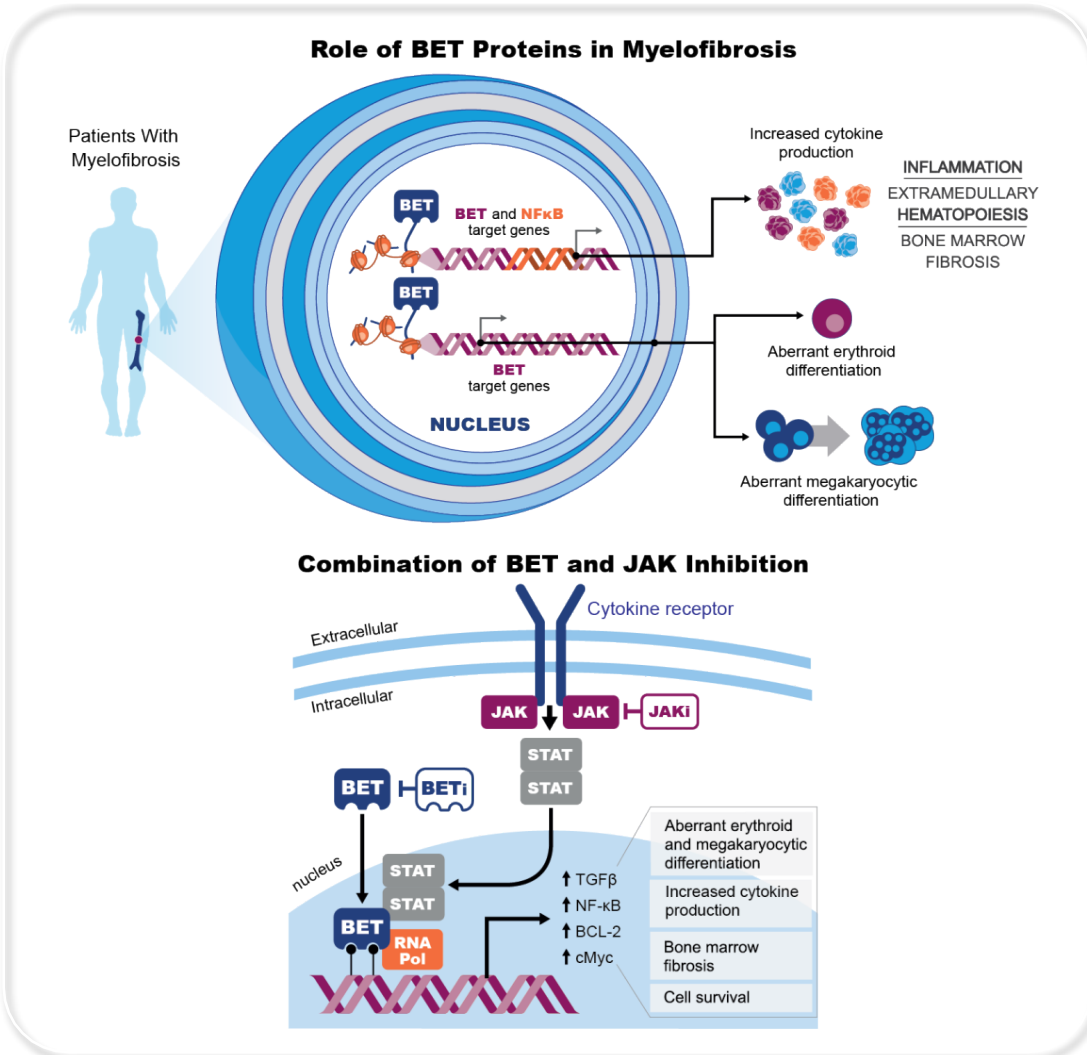
# **Pelabresib (CPI-0610) Combined With Ruxolitinib for JAK Inhibitor Treatment-Naïve Patients With Myelofibrosis: Durability of Response and Safety Beyond Week 24**

**John Mascarenhas,<sup>1</sup> Marina Kremyanskaya,<sup>1</sup> Andrea Patriarca,<sup>2</sup> Vikas Gupta,<sup>3</sup> Francesca Palandri,<sup>4</sup> Timothy Devos,<sup>5</sup> Raajit K Rampal,<sup>6</sup> Moshe Talpaz,<sup>7</sup> Alessandro Vannucchi,<sup>8</sup> Andrew Kuykendall,<sup>9</sup> Jean-Jacques Kiladjian,<sup>10</sup> Srdan Verstovsek,<sup>11</sup> Ruben Mesa,<sup>12</sup> Gozde Colak,<sup>13</sup> Qing Li,<sup>14</sup> Sandra Klein,<sup>13</sup> Claire Harrison,<sup>15</sup> on behalf of the MANIFEST study investigators.**

<sup>1</sup>Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; <sup>2</sup>Hematology Unit, Department of Translational Medicine, University of Eastern Piedmont and AOU Maggiore della Carità, Novara, Italy; <sup>3</sup>Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; <sup>4</sup>IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia “Seràgnoli”, Bologna, Italy; <sup>5</sup>University Hospitals Leuven and Laboratory of Molecular Immunology (Rega Institute), KU Leuven, Leuven, Belgium; <sup>6</sup>Memorial Sloan-Kettering Cancer Center, New York, NY; <sup>7</sup>University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; <sup>8</sup>University of Florence, Azienda Ospedaliero-Universitaria Careggi, CRIMM, Florence, Italy; <sup>9</sup>Moffitt Cancer Center, Tampa, FL; <sup>10</sup>Hôpital Saint-Louis, Université de Paris, Paris, France; <sup>11</sup>Leukemia Department, University of Texas MD Anderson Cancer Center, Houston, TX; <sup>12</sup>Mays Cancer Center at UT Health San Antonio MD Anderson Cancer Center, San Antonio, TX; <sup>13</sup>Constellation Pharmaceuticals, Inc., a MorphoSys Company, Boston, MA; <sup>14</sup>MorphoSys US, Inc., Boston, MA; <sup>15</sup>Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom.

# Simultaneous inhibition of BET and JAK in myelofibrosis

A potential therapeutic approach to address heterogenous disease pathology



- JAK inhibition with ruxolitinib is the standard of care in patients with higher risk MF who are ineligible for HSCT, but unmet medical need persists due to limited efficacy with currently available JAKi monotherapy, high rates of discontinuation and toxicities<sup>1</sup>
- Preclinical data indicated synergistic effects of BET and JAK inhibition in MF<sup>2</sup>
- Pelabresib, a BET inhibitor, downregulates the expression of genes that contribute to the heterogenous pathology of MF<sup>3-7</sup>

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BET, bromodomain and extraterminal domain; JAK, Janus kinase; NF-κB, nuclear factor kappa B; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor β.

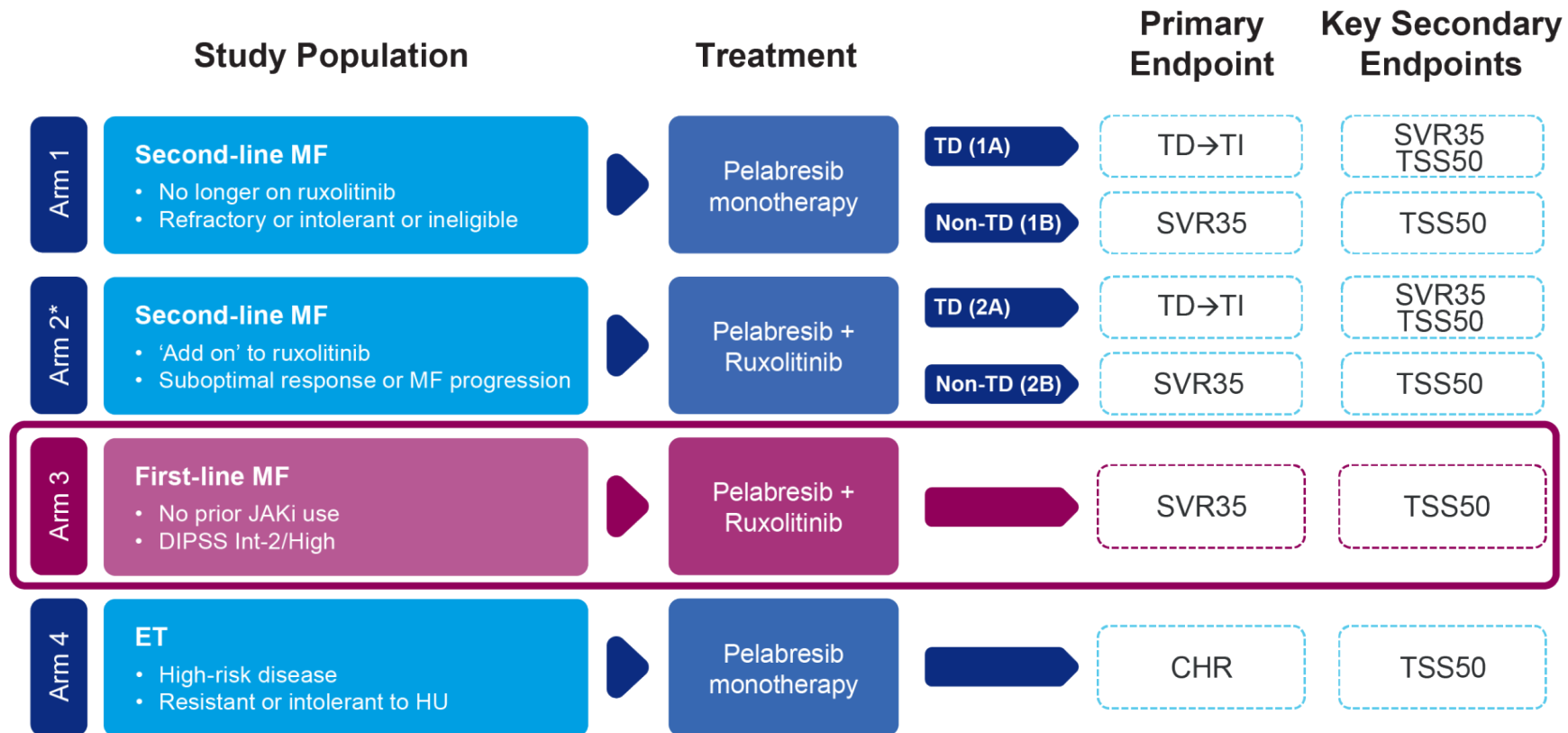
1. Verstovsek S, et al. *Haematologica* 2015;100:479–488; 2. Kleppe M, et al. *Cancer Cell* 2018;33:29–43.e7; 3. Stratton MS, et al. *F1000Res* 2017;6:F1000 Faculty Rev–1015; 4. Ding N, et al. *PNAS* 2015;112:15713–15718;

5. Ceribelli M, et al. *PNAS* 2014;111:11365–11370; 6. Tefferi A, et al. *J Clin Oncol* 2011;29:573–582; 7. Keller P, et al. *Hemasphere* 2021;5(Suppl 2):515.

Mascarenhas J, et al. ASH 2022. Abstract 238

**Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority**

# MANIFEST: Ongoing, global, open-label Phase 2 study investigating pelabresib in myelofibrosis and essential thrombocythemia



\*Pelabresib (CPI-0610) as Add-on to Ruxolitinib in Myelofibrosis: Durability of Response and Safety Beyond Week 24 in the Phase 2 MANIFEST Study — Harrison C, et al. Poster presentation 4344, Dec 12, 6:00–8:00 pm EST

CHR, complete hematologic response; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; HU, hydroxyurea; Int-2, intermediate-2; JAKi, Janus kinase inhibitor; SVR35, ≥35% reduction in spleen volume at Week 24; TD, transfusion dependent; TI, transfusion independent; TSS50, ≥50% reduction in total symptom score at Week 24.

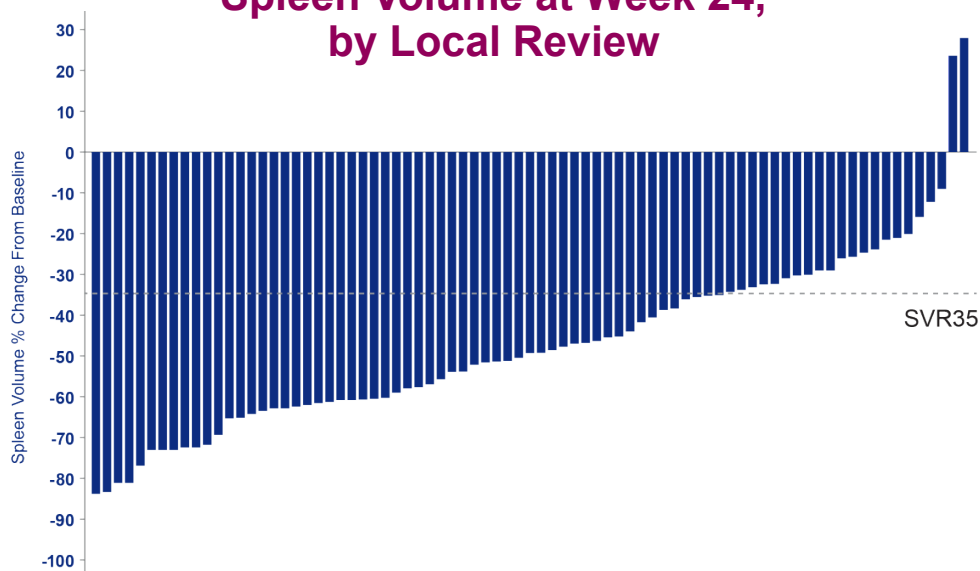
Clinicaltrials.gov. NCT02158858. Available at: <https://clinicaltrials.gov/ct2/show/NCT02158858>. Accessed November 10, 2022.

Mascarenhas J, et al. ASH 2022. Abstract 238

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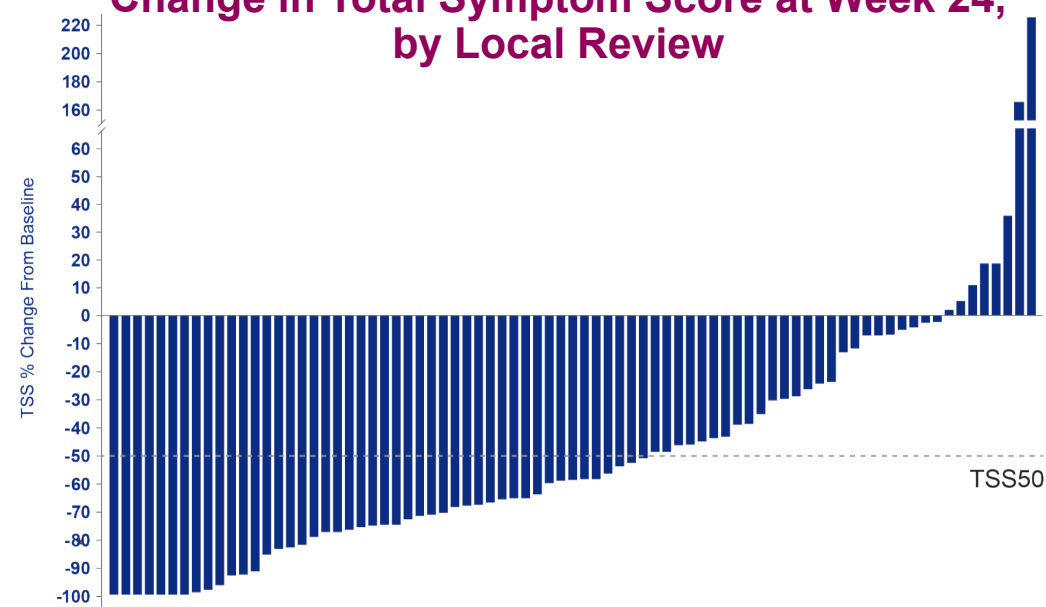
# MANIFEST Arm 3 Results

## Spleen Volume at Week 24, by Local Review



N=84		
<b>SVR35 at Wk 24</b>	<b>68% (57/84)</b>	95% CI 57–78
Median % SVR	–50%	
Mean % SVR	–48%	
<b>SVR35 at any time</b>	<b>80% (67/84)</b>	95% CI 70–88

## Change in Total Symptom Score at Week 24, by Local Review



N=84	
<b>TSS50 at Week 24</b>	<b>56%</b> (46/82*), 95% CI 45–67
Median TSS % change	–59%
Mean TSS % change	–47%
<b>TSS50 at any time</b>	<b>83%</b> (68/82*), 95% CI 73–90

# The Combination of Navitoclax and Ruxolitinib in JAK Inhibitor-Naïve Patients With Myelofibrosis Mediates Responses Suggestive of Disease Modification

Francesco Passamonti<sup>1</sup>, James Foran<sup>2</sup>, Anand Tandra<sup>3</sup>, Valerio De Stefano<sup>4,5</sup>, Maria Laura Fox<sup>6</sup>, Ahmad Mattour<sup>7</sup>, Mary Frances McMullin<sup>8</sup>, Andrew C. Perkins<sup>9</sup>, Gabriela Rodriguez-Macías<sup>10</sup>, Hassan Sibai<sup>11</sup>, Qin Qin<sup>12</sup>, Yan Sun<sup>12</sup>, Jalaja Potluri<sup>12</sup>, Jason Harb<sup>12</sup>, Jonathan How<sup>13</sup>

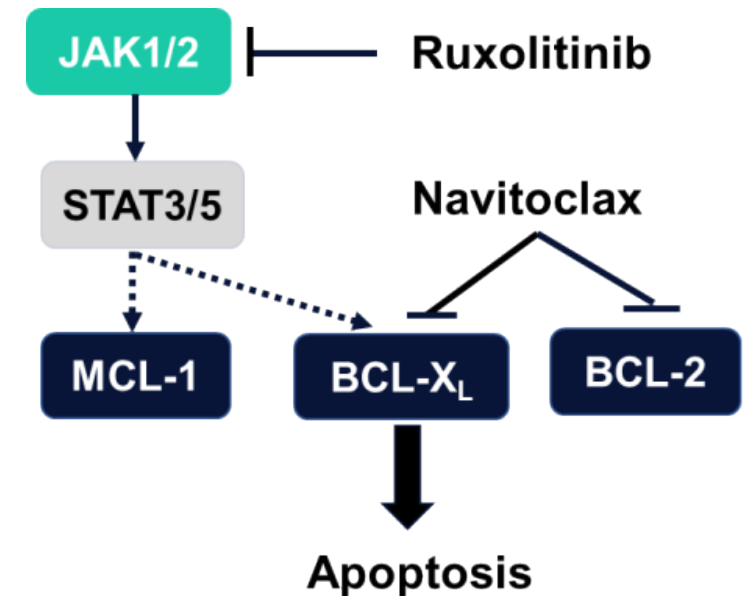
<sup>1</sup>Department of Medicine and Surgery, University of Insubria, Varese, Italy; <sup>2</sup>Mayo Clinic, Jacksonville, FL, USA; <sup>3</sup>Indiana Blood and Marrow Transplant, Indianapolis, IN, USA; <sup>4</sup>Section of Hematology, Department of Radiological and Hematological Sciences, Catholic University, Rome, Italy; <sup>5</sup>Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; <sup>6</sup>Department of Hematology, Hospital Universitari Vall d'Hebron, Experimental Hematology, Vall d'Hebron Institute of Oncology, Vall d'Hebron Hospital Campus, Barcelona, Spain; <sup>7</sup>Henry Ford Hospital, Detroit, MI, USA; <sup>8</sup>Center for Medical Education, Queen's University Belfast, Belfast, UK; <sup>9</sup>Australian Centre for Blood Diseases, Monash University and The Alfred Hospital, Melbourne, Australia; <sup>10</sup>Department of Hematology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; <sup>11</sup>Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada; <sup>12</sup>AbbVie Inc., North Chicago, IL, USA; <sup>13</sup>Division of Hematology, McGill University Health Center, Montreal, Canada



# The combination of navitoclax and ruxolitinib may offer a new treatment option for patients with myelofibrosis

**Patients with myelofibrosis (MF) are currently treated with Janus kinase inhibitors that reduce splenomegaly and constitutional symptoms but exert little effect on bone marrow fibrosis or variant allele frequency for driver mutations<sup>1</sup>**

- Pro-survival BCL-2 proteins, including BCL-X<sub>L</sub> is overexpressed in patient cells with myeloproliferative neoplasms, including MF<sup>2</sup>
- Ruxolitinib suppresses the transcription of BCL-X<sub>L</sub> and MCL-1, leading to decreased levels of these proteins, and navitoclax inhibits the antiapoptotic activity of BCL-X<sub>L</sub> and BCL-2; in preclinical studies, the synergy between navitoclax and JAK1/2 inhibitors has been shown to induce death of malignant cells<sup>3,4,5</sup>
- The addition of navitoclax to ruxolitinib in patients with suboptimal responses to ruxolitinib monotherapy has demonstrated preliminary efficacy and safety, and evidence of disease modification<sup>1,6</sup>

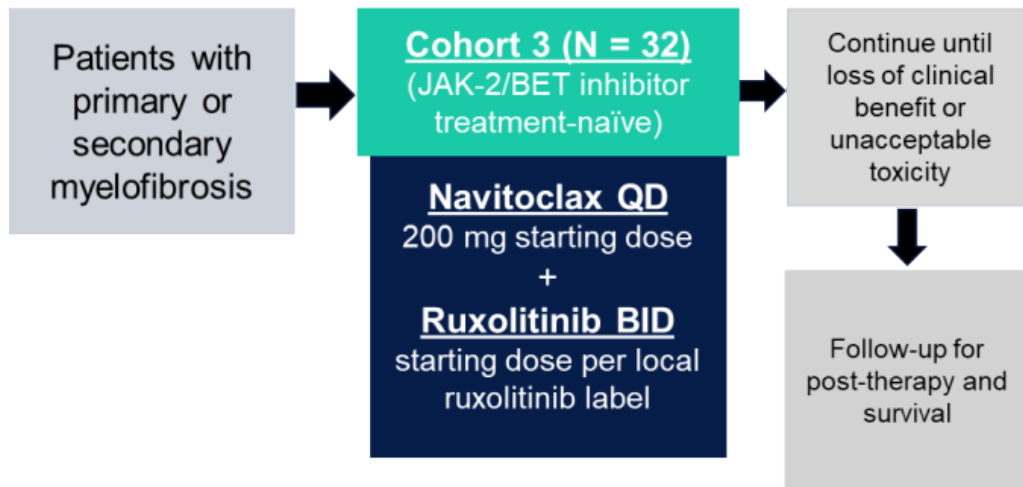


<sup>1</sup> Pemmaraju et al, Lancet Oncol, 2022; <sup>2</sup> Tognon et al, J. Hematol. Oncol; <sup>3</sup> Guo et al, Plos One, 2015; <sup>4</sup> Breccia et al, Ann Hematol, 2017; <sup>5</sup> Refici et al, AACR, 2022; <sup>6</sup> Harrison et al, J Clin Oncol, 2022.



# Cohort 3 of the REFINE study enrolled JAKi-naïve patients with MF

## Phase II REFINE Study Design (NCT03222609)



Patients initiated navitoclax at 100 mg QD or 200 mg QD if baseline platelet count was  $\leq 150 \times 10^9/L$  or  $> 150 \times 10^9/L$ , respectively

### Key inclusion criteria

- Age  $\geq 18$  years
- Primary or secondary MF with splenomegaly (DIPSS  $\geq$  Intermediate-1)
- ECOG score 0-2
- JAK-2 or BET inhibitor treatment-naïve

### Key exclusion criteria

- Splenic irradiation  $\leq 6$  months or splenectomy
- $> 10\%$  blasts in peripheral blood or bone marrow aspirate
- Prior therapy with a BH-3 mimetic compound or stem cell transplantation
- Platelet count  $< 100 \times 10^9/L$

### Primary endpoint

- SVR<sub>35</sub> from baseline at week 24 assessed by MRI or CT reviewed centrally

### Key secondary/exploratory endpoints

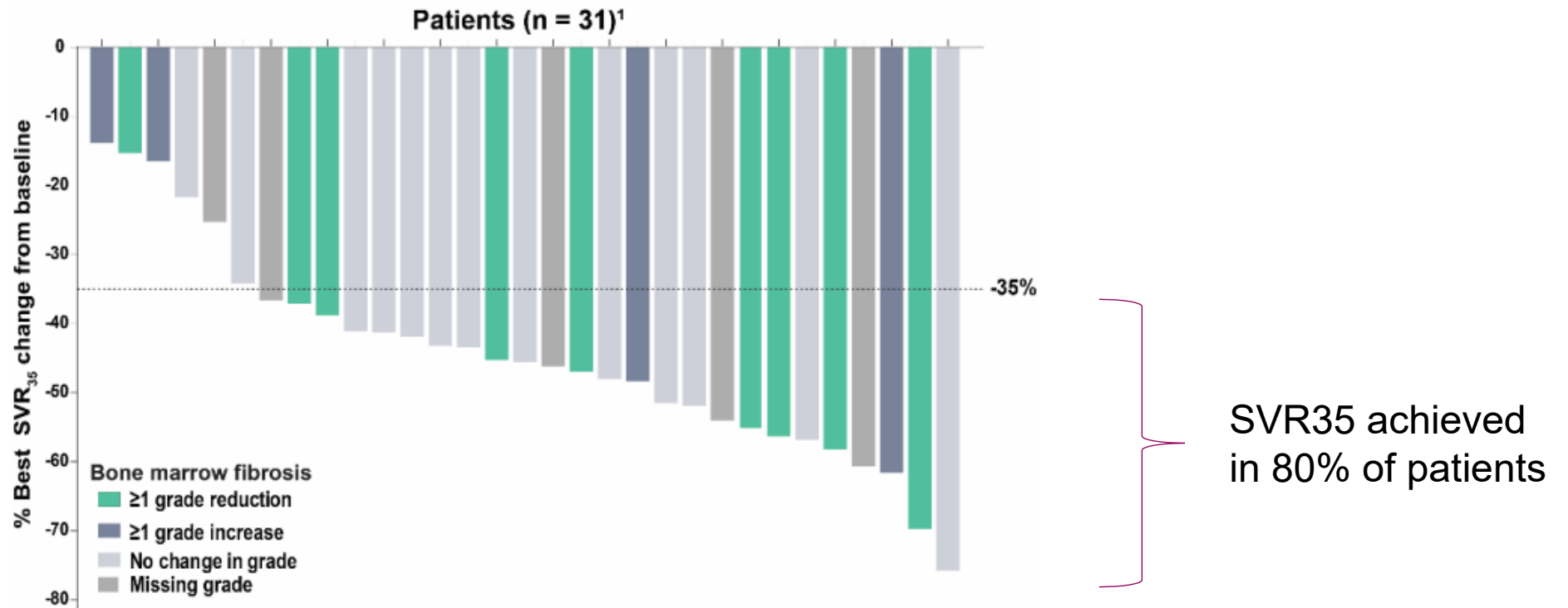
- Change in BMF grade from baseline reviewed locally
- Reduction in VAF for driver mutations determined centrally<sup>1</sup>

Abbreviations: BMF, bone marrow fibrosis; DIPSS, Dynamic International Prognostic Scoring System; ECOG, Eastern Cooperative Oncology Group; MF, myelofibrosis; SVR, spleen volume reduction; VAF, variant allele frequency

<sup>1</sup> Driver gene VAF and high molecular risk mutations were determined in whole blood using a 50 gene focus myeloid next-generation sequencing panel (Interspace Pharma Solutions, Morrisville, NC, USA)



# Spleen Volume Reduction and Bone Marrow Fibrosis

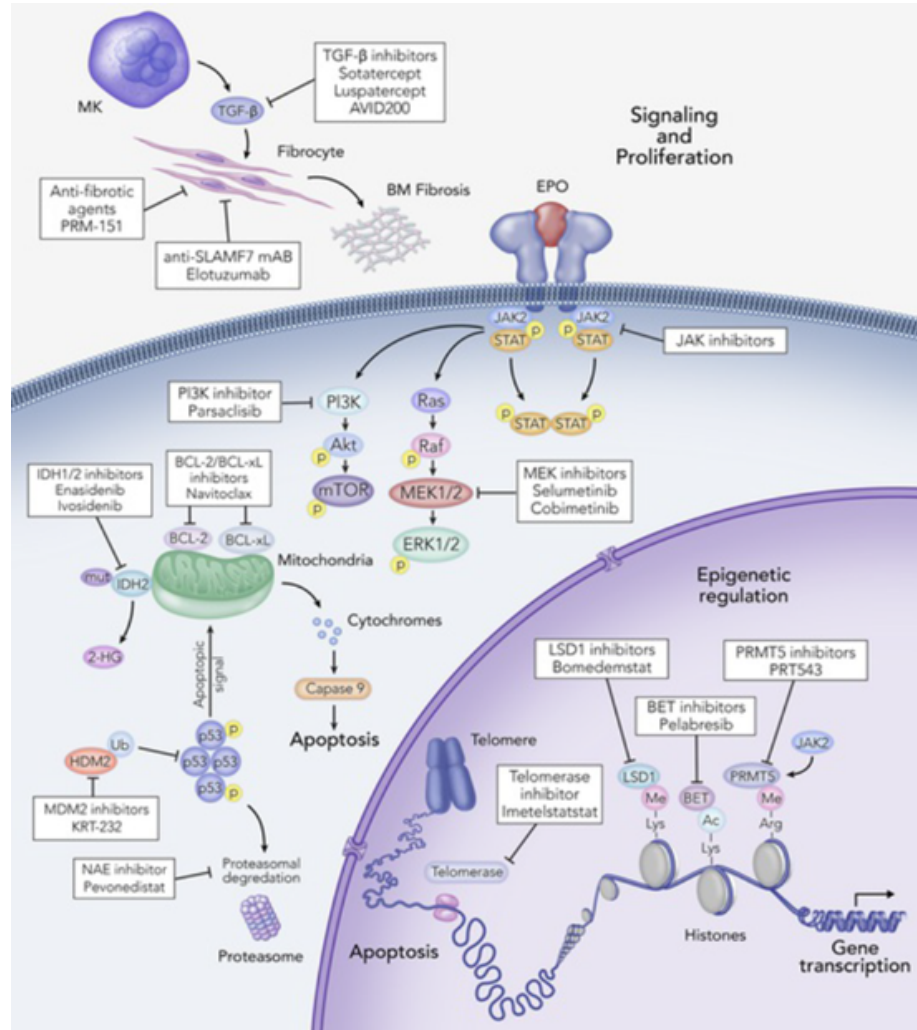


- At any time during study treatment, 9/32 (28%) patients achieved  $\geq 1$  grade reduction in BMF
- Complete resolution of BMF was observed in 2/9 (22%) patients; their baseline BMF grades were 2 and 3
- The median time to BMF reduction was 12.3 weeks (range, 12.1 – 24.1)
- At any time during study treatment, 8/25 (32%) patients with SVR<sub>35</sub> also achieved  $\geq 1$  grade reduction in BMF

# Ongoing questions/issues in MF

- Combine JAKi + non-JAKi therapies upfront, or save combinations for later-line settings?
  - Are risks of combinations (cytopenias, GI) worth potential benefits in the frontline setting?
  - Will faster/deeper responses lead to better outcomes?
- What should our goals/endpoints be?
  - Move away from SVR35 and towards quality of life, length of life?
  - Other surrogates: Molecular responses? Fibrosis improvements?

# Other Novel Non-JAKi Therapies for MPNs



- Other signaling pathway inhibitors
- Epigenetic agents
- TGFβ inhibitors
- Anti-fibrosing agents
- **Mutant CALR-directed mAB**



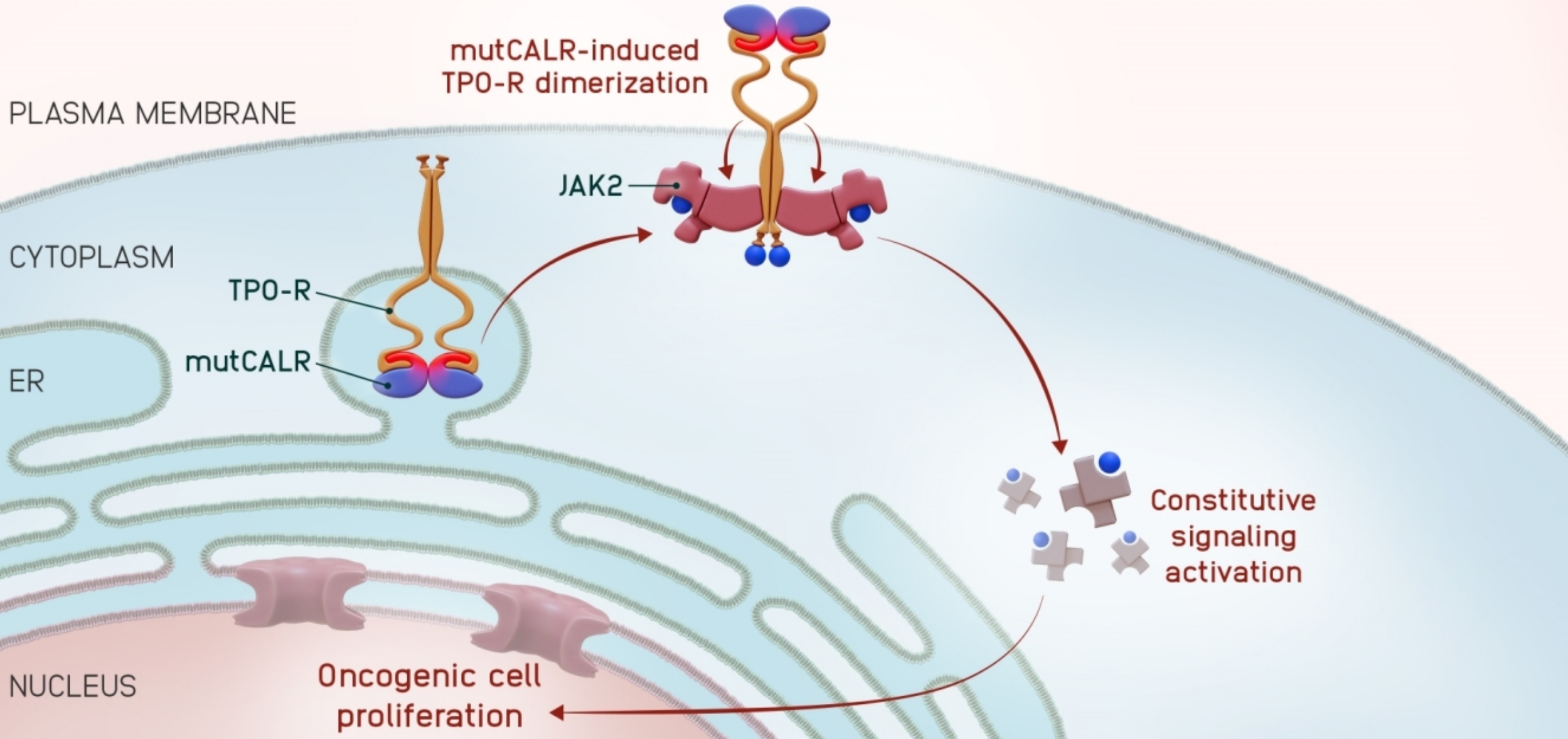
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# Discovery of INCA033989, a Monoclonal Antibody That Selectively Antagonizes Mutant Calreticulin Oncogenic Function in Myeloproliferative Neoplasms

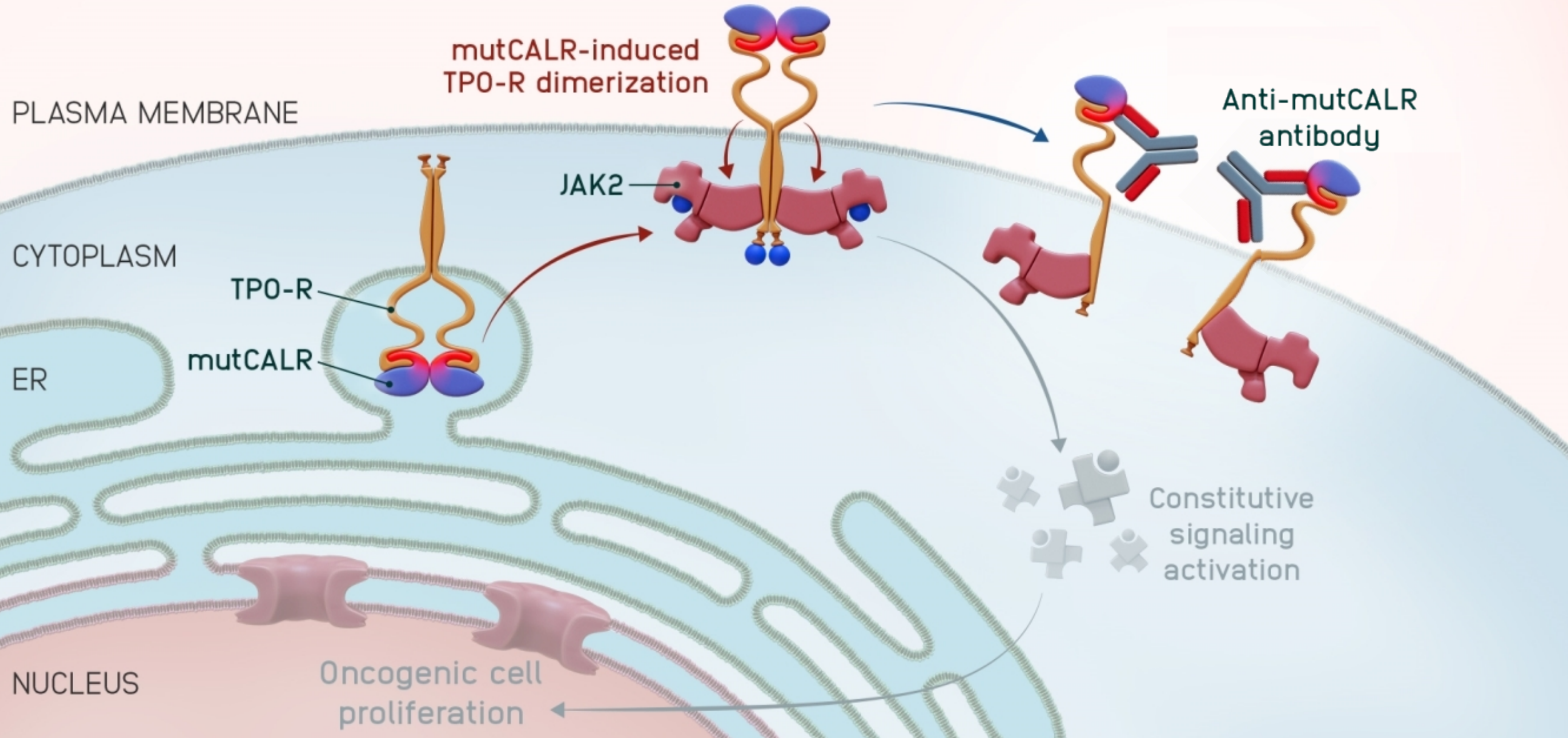
**Edimara Reis**<sup>1</sup>, Rebecca Buonpane<sup>1</sup>, Hamza Celik<sup>1</sup>, Caroline Marty<sup>2</sup>, Angela Lei<sup>1</sup>, Fatoumata Jobe<sup>1</sup>, Mark Rupar<sup>1</sup>, Yue Zhang<sup>1</sup>, Darlise DiMatteo<sup>1</sup>, Rahel Awdew<sup>1</sup>, William Vainchenker<sup>2</sup>, Jing Zhou<sup>1</sup>, Ian Hitchcock<sup>3</sup>, Isabelle Plo<sup>2</sup>, Horacio Natri<sup>1</sup>, Patrick Mayes<sup>1</sup>

<sup>1</sup>Incyte Corporation, Wilmington, DE, USA; <sup>2</sup>INSERM UMR 1287, Université Paris-Saclay, Gustave Roussy, Villejuif, France; <sup>3</sup>York Biomedical Research Institute, Department of Biology, University of York, York, UK

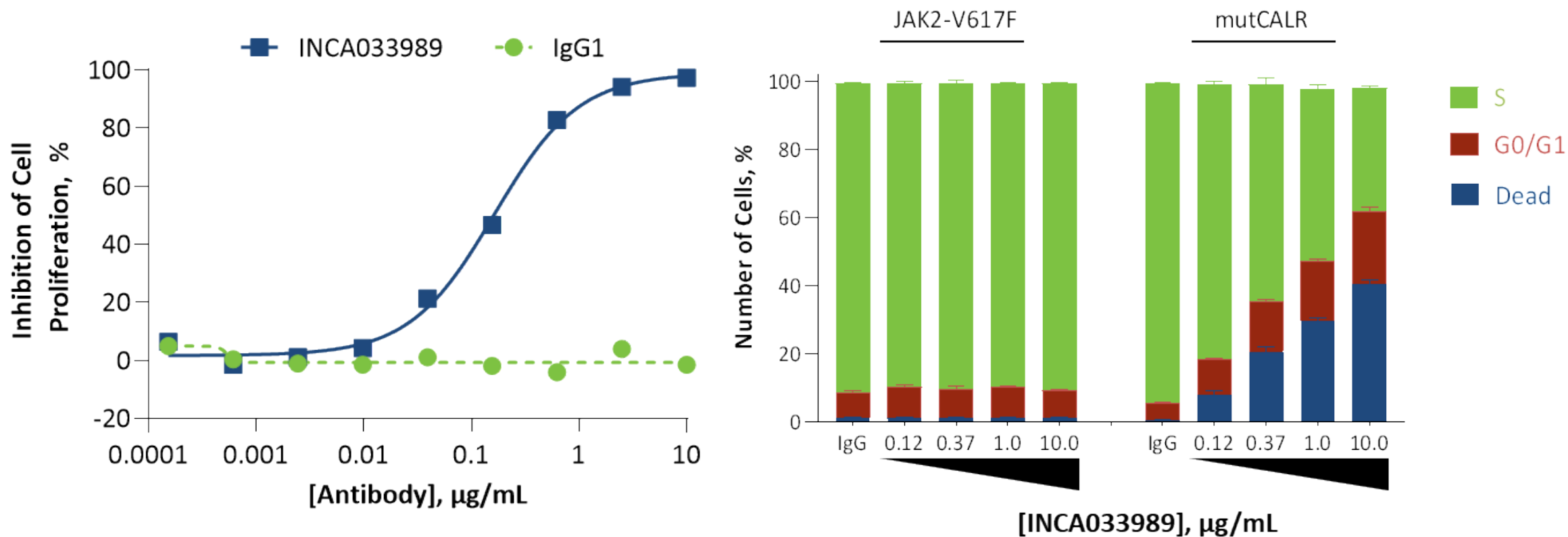
# Mutant calreticulin (mutCALR) induces oncogenic cell proliferation



# Anti-mutCALR antibody selectivity inhibits oncogenic cell proliferation

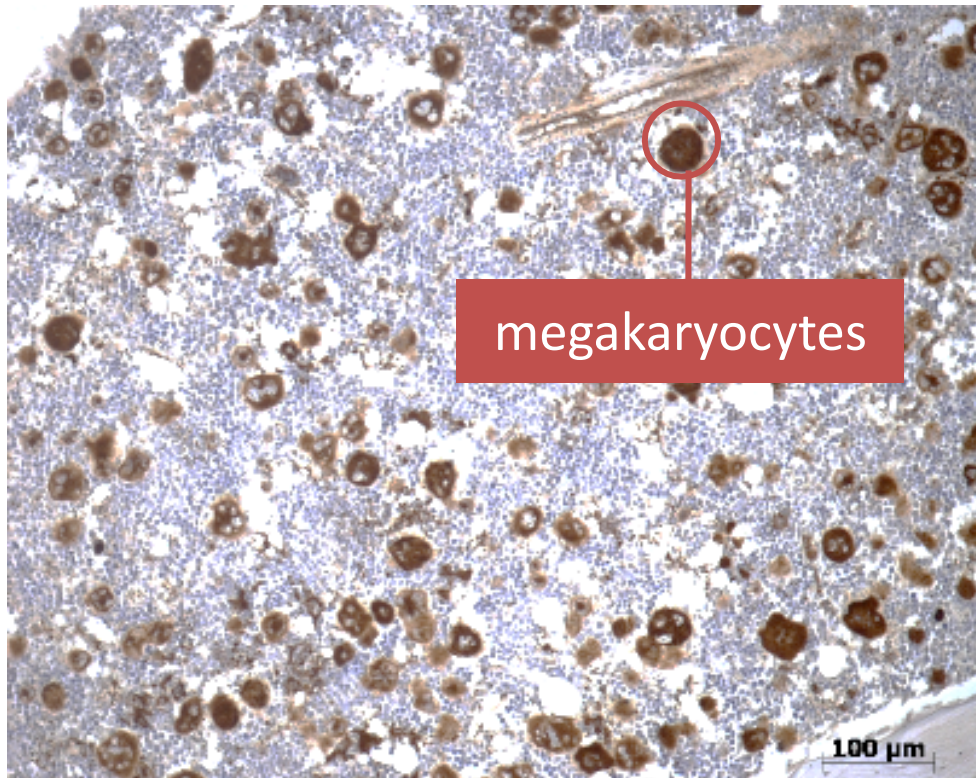


# INCA033989 selectively inhibits cell proliferation and induces death of mutCALR<sup>+</sup> cells

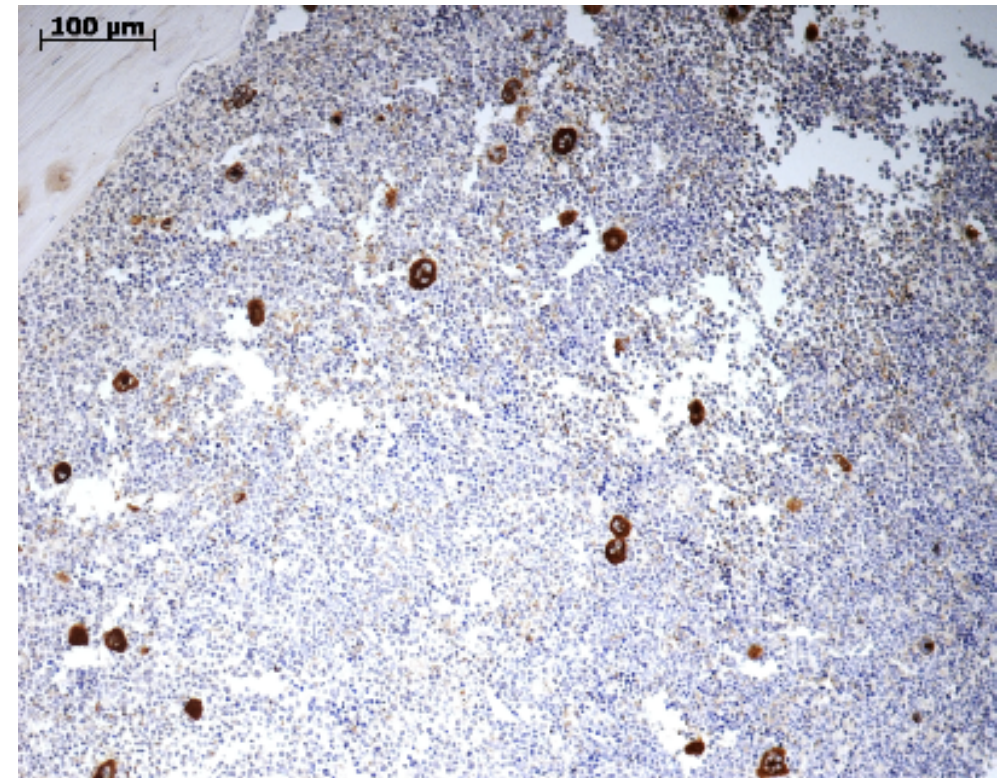


# INCA033989 surrogate treatment re-establishes normal megakaryopoiesis

**Isotype**



**INCA033989 (mouse surrogate)**



Megakaryocytes stained with anti-von Willebrand factor antibody.

Caroline Marty, Elodie Rosa, Maxime Evrard, William Vainchenker, Isabelle Plo. Gustave Roussy Institute, INSERM, Université Paris-Saclay.

# Case 3: Polycythemia Vera

## 46 yo M presents with headaches and pruritus

- No significant medical history, no history of thrombosis
- Labs: WBC 11.3k, Hb 18.2 g/dL, Hct 54%, platelets 455k
- Erythropoietin <1
- PCR: JAK2 V617F+

Diagnosed with PV, low risk. Started on ASA 81 mg/day and therapeutic phlebotomy to goal Hct <45%. 6 months later, he is still requiring frequent therapeutic phlebotomy, serum ferritin is down to 3, and he is feeling more fatigued.

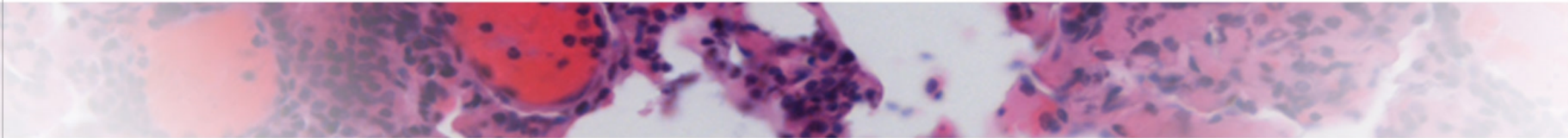
What are the management options for symptomatic, low risk PV?

- Cytoreductive agents: Hydroxyurea, Peg-Interferon alpha, Ropeginterferon alpha 2b
- Investigational agents: Rusfertide (hepcidin analog)





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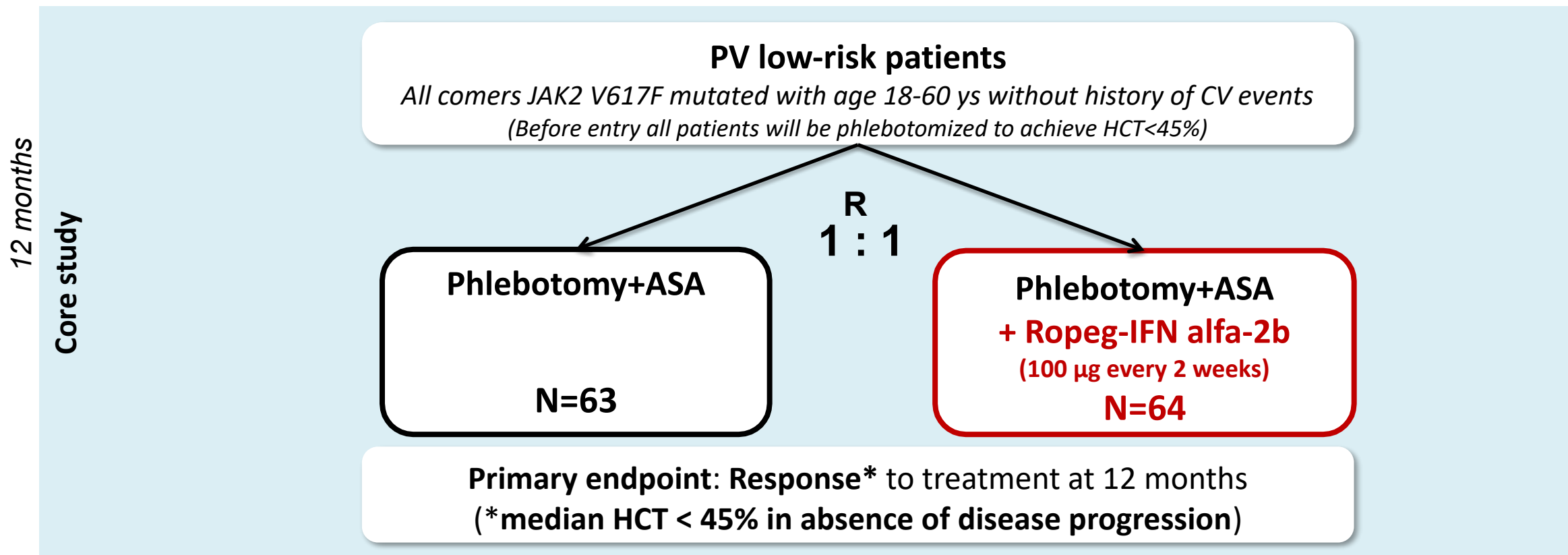


# Ropeginterferon Alfa-2b Versus Standard Therapy for Low-Risk Patients with Polycythemia Vera. **Final Results of Low-PV Randomized Phase II Trial**

**Tiziano Barbui, MD**

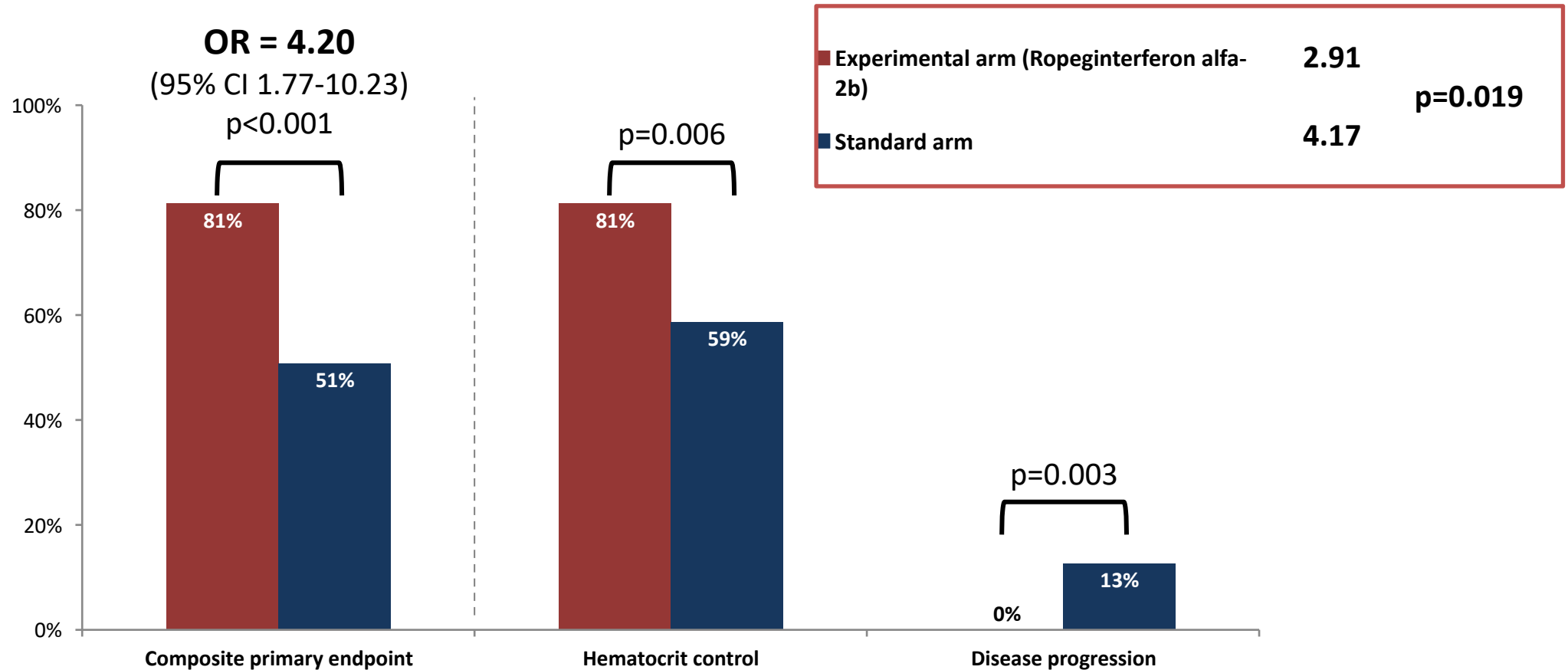
FROM Research Foundation, Papa Giovanni XXIII hospital  
Bergamo, ITALY

# Core study (intention-to-treat analysis)



# Core study: primary endpoint

Mean number of  
phlebotomy per pat/year:



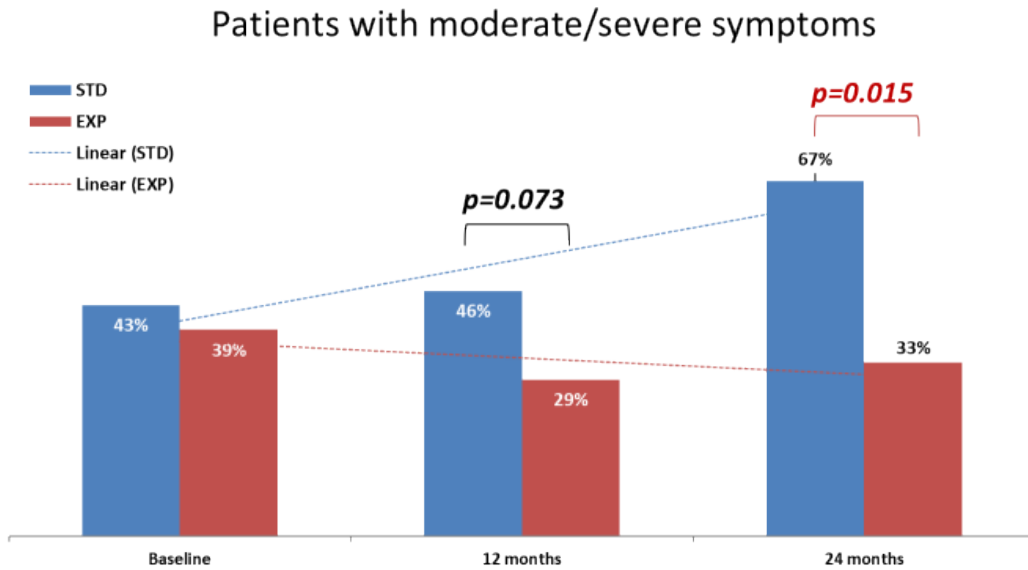
**Disease progression** was observed in **8 patients** (all in standard arm):

- In 6, platelet count progression to  $>1000 \times 10^9/L$  in pts with baseline values lower than  $600 \times 10^9/L$ .
- In 2, splenic infarction and transient ischemic attack, respectively

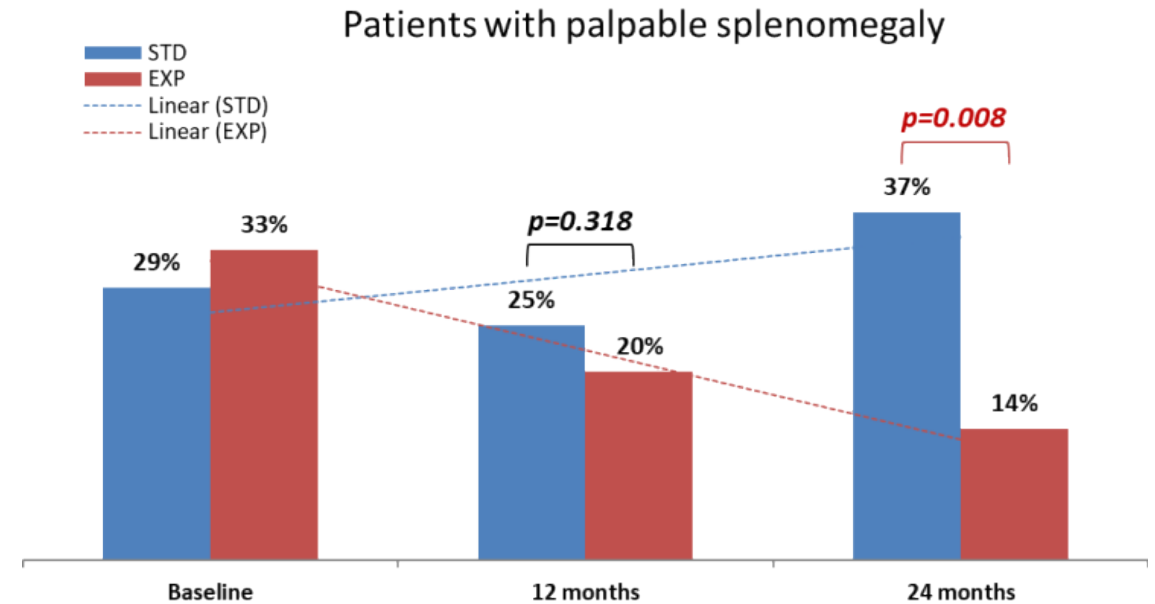


# Responders: Other Endpoints

## Overall quality of life\*

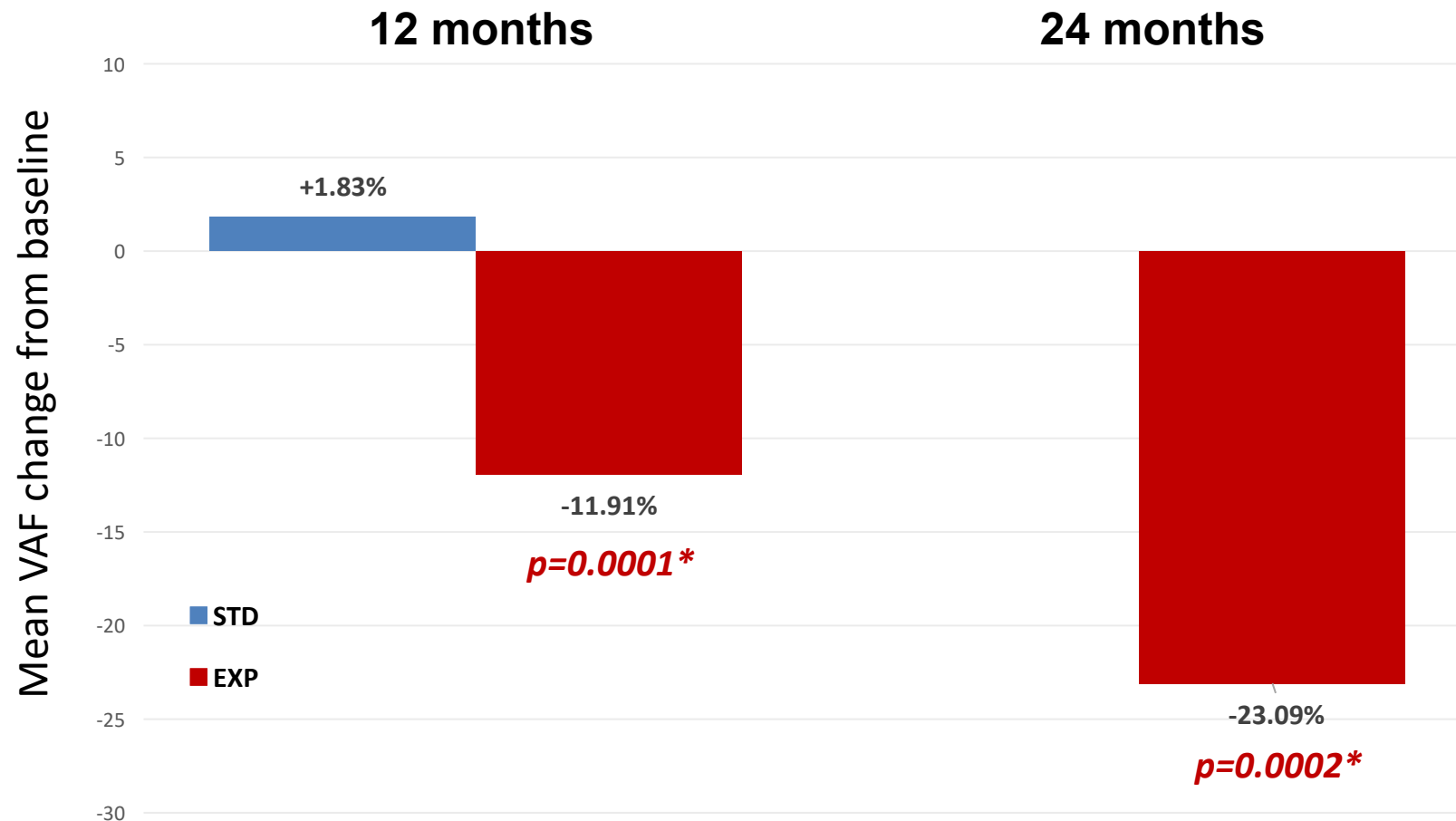


## Percent with splenomegaly



\* Mesa R et al, Clin Lymphoma Myeloma Leuk. 2018

# Responders: *JAK2V617F* VAF



\* Statistical differences from baseline (paired t-test)



# Safety

	Ropeg	Phlebotomy	p
	<i>N=87*</i>	<i>N=72*</i>	
Patients with AE	73 (84%)	36 (50%)	<.001
Patients with treatment-related AE	48 (55%)	4 (6%)	<.001
Patients with grade 3 or 4 <sup>§</sup> AE	8 (9%)	6 (8%)	0.948
AE that caused therapy discontinuation	7 (8%)	0 (0%)	0.016

\* AE are counted under the treatment actually received (i.e., *n*=87 patients received RopegInt alfa-2b, *n*=64 since randomization and *n*=23 after crossover, respectively. *N*=72 patients received phlebotomy-only, *n*=63 since randomization and *n*=9 after crossover, respectively).

§ Only one grade 4 AE (hypertriglyceridemia), occurred under Ropeg



# Chronic Myeloid Leukemia

- Now 6 approved BCR/ABL-targeted agents for CML:
  - Imatinib
  - Dasatinib
  - Nilotinib
  - Bosutinib
  - Ponatinib
  - Asciminib (approved 2021)
- Ongoing question: How to manage those with suboptimal response?



# Efficacy and Safety Results From ASC4MORE, a Randomized Study of Asciminib Add-On to Imatinib, Continued Imatinib, or Switch to Nilotinib in Patients With Chronic-Phase Chronic Myeloid Leukemia Not Achieving Deep Molecular Responses With $\geq 1$ Year of Imatinib

Jorge E. Cortes,<sup>1</sup> Timothy P. Hughes,<sup>2</sup> Jan Geissler,<sup>3</sup> Dong-Wook Kim,<sup>4</sup> Elza Lomaia,<sup>5</sup> Jiri Mayer,<sup>6,7</sup> Anna Turkina,<sup>8</sup> Sarah Hurwicz Kogut,<sup>9</sup> Ana Paula Cardoso,<sup>10</sup> Monali Sura,<sup>10</sup> Giuseppe Saglio<sup>11</sup>



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- Oral presentation slides
- Supplementary material
- Author video
- Visual infographic

<https://bit.ly/CortesJ80>

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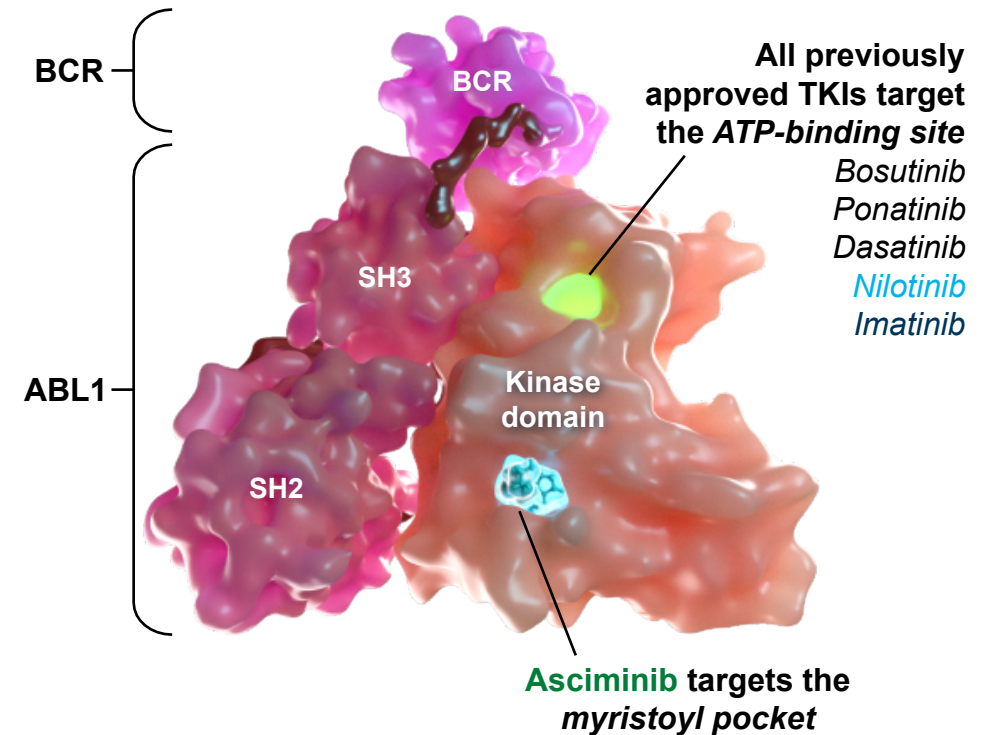
# Introduction

- For patients with CML-CP, TKIs have led to a life expectancy similar to the general population, making **quality of life and TFR important treatment goals**<sup>1,2</sup>
- In 1L, **30% to 60% of patients will not achieve DMRs** with second generation TKIs after 5 years of therapy, with fewer imatinib-treated patients achieving DMRs<sup>3-5</sup>
- **Safe and effective treatment options are needed in early lines** to help more patients achieve their treatment goals
- **Asciminib** was first **approved** in the United States for the treatment of adults with Ph+ CML-CP previously treated with  $\geq 2$  TKIs<sup>a</sup> and those with Ph+ CML-CP and the T315I mutation, with subsequent approvals worldwide<sup>6</sup>
- **Here we report data from the ASC4MORE study of asciminib add-on to imatinib vs continued imatinib vs switch to nilotinib in patients with CML-CP who have received imatinib for  $\geq 1$  year without achieving DMRs**

1L, first line; ATP, adenosine triphosphate; CML, chronic myeloid leukemia; CP, chronic phase; DMR, deep molecular response; Ph, Philadelphia chromosome; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

<sup>a</sup> This approval was based on efficacy and safety data from the ASCSEMBL study.

Asciminib is the first BCR::ABL1 inhibitor to **Specifically Target the ABL Myristoyl Pocket (STAMP)<sup>6,7</sup>**



# ASC4MORE Study Design

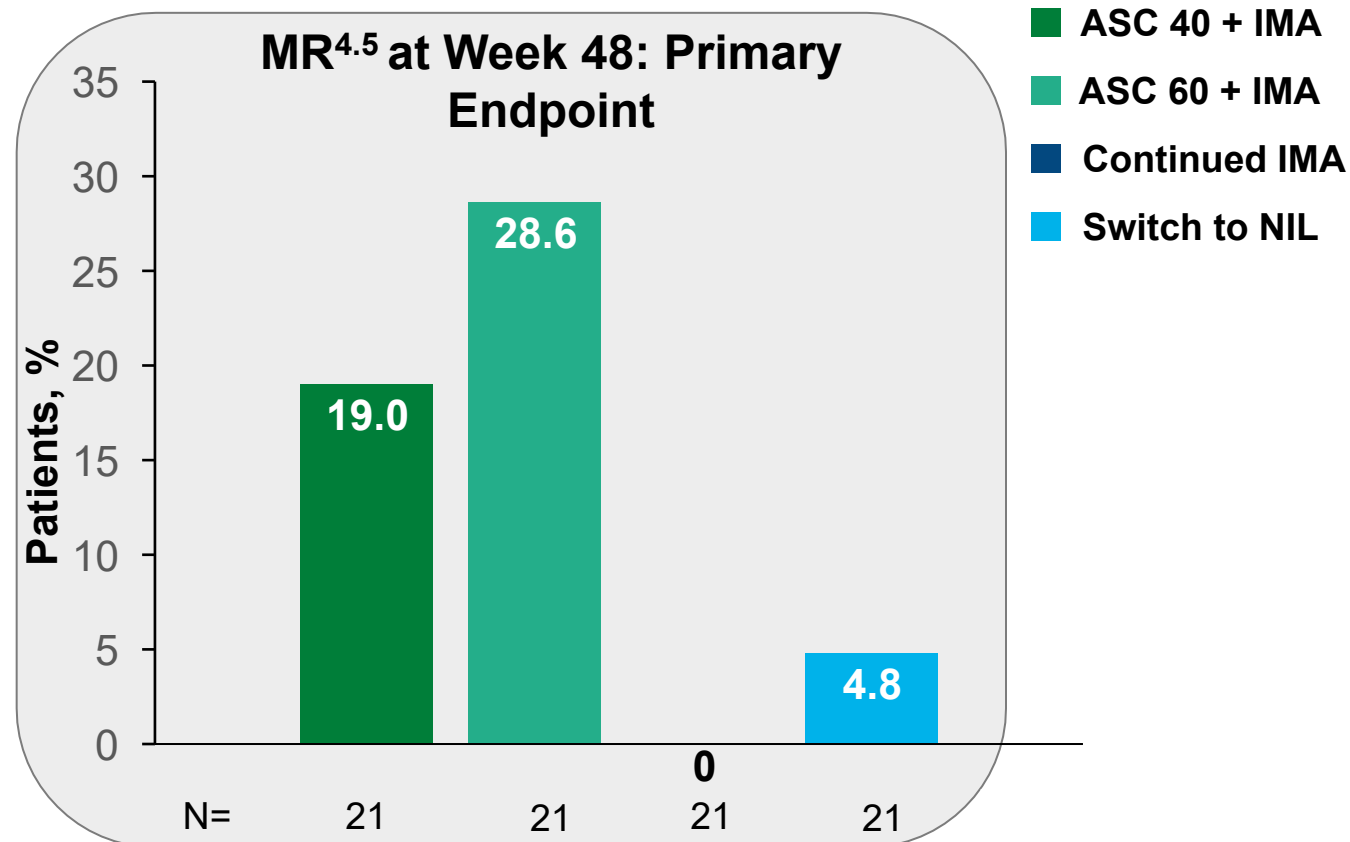


BID, twice daily; IS, International Scale; MR<sup>4.5</sup>,  $BCR::ABL1^{IS} \leq 0.0032\%$ ; PTA, post-trial access; QD, once daily.

<sup>a</sup> With no change of dose in the past 3 months. <sup>b</sup> The monotherapy arm was added in a protocol amendment on July 12, 2022 to estimate the safety and efficacy of single agent asciminib and is now enrolling. <sup>c</sup> Patients may discontinue treatment at the time of interim analysis if there is excessive toxicity without added benefit is observed in 1 of the observational arms. Patients who choose to discontinue in the asciminib 60 mg add-on arm will have the opportunity to continue the study in the asciminib 40 mg add-on arm if the investigator believes it is in the best interest of the patient.

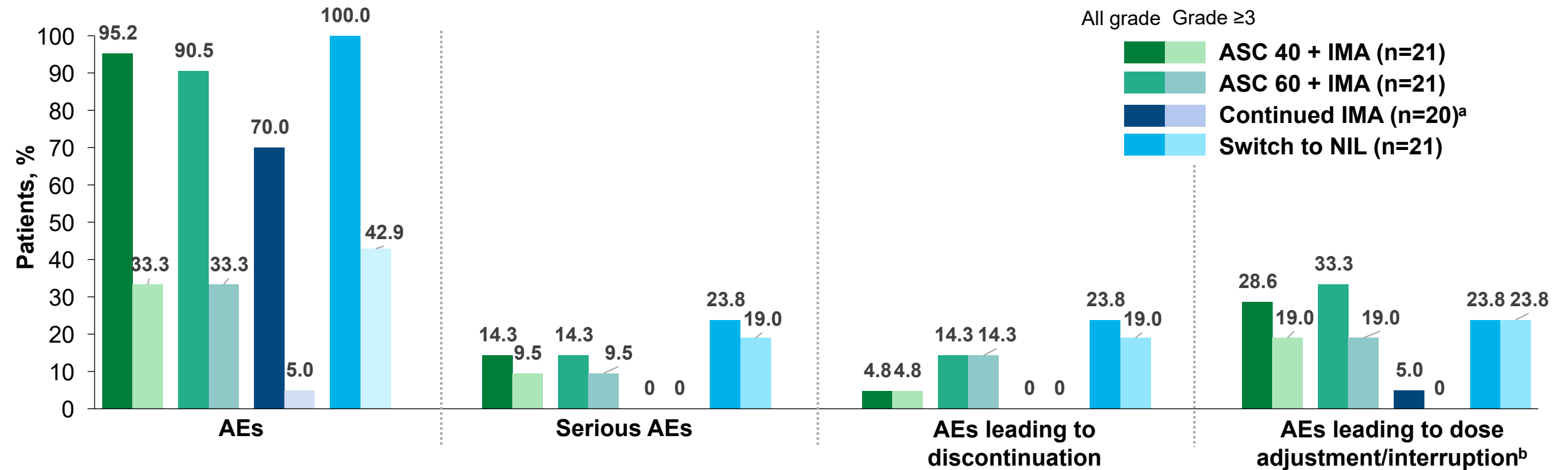
<sup>d</sup> Crossover allowed for patients who have not achieved MR<sup>4.5</sup> (not included in this analysis).

# MR<sup>4.5</sup> at Weeks 24 and 48



- More patients were able to achieve MR<sup>4.5</sup> with **asciminib add-on** to imatinib vs continued **imatinib** or switch to **nilotinib**
- No patients in the continued **imatinib** arm were in MR<sup>4.5</sup> at week 48, although more patients in this arm were in MMR at baseline than in the **asciminib add-on** arms

# Overview of AEs

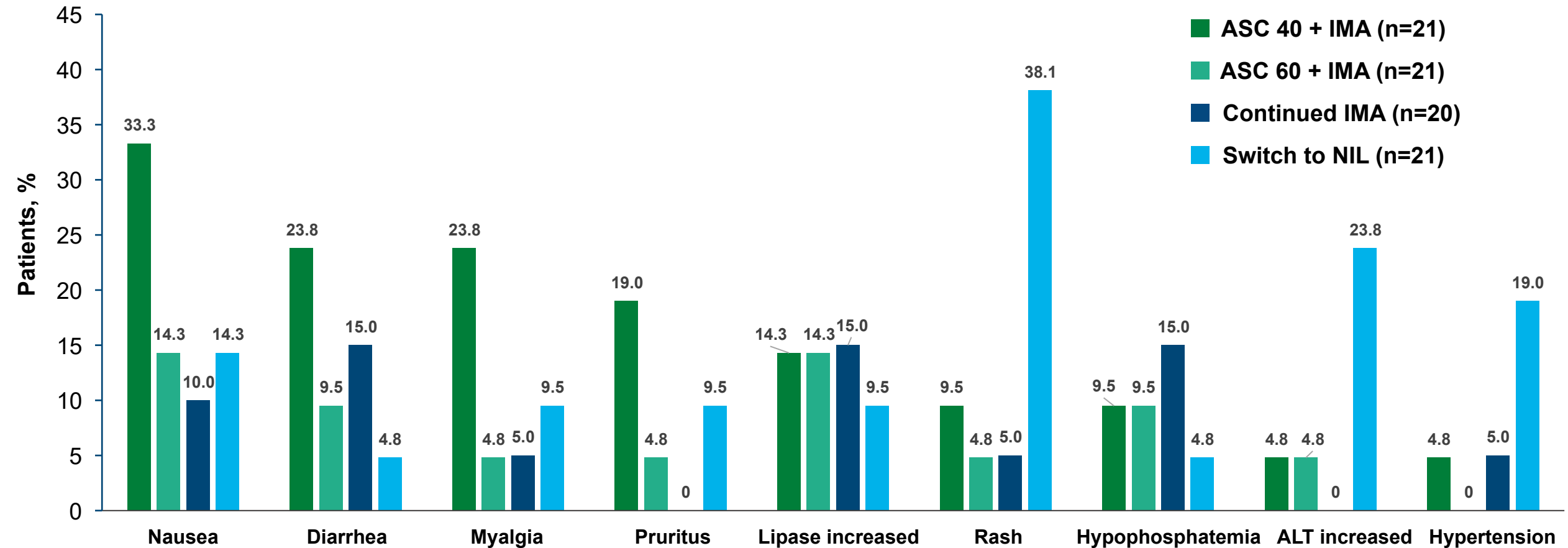


- With longer median (range) durations of exposure (104.7 [27-160], 94.0 [1-148], 53.4 [50-142], and 78.9 [1-146] weeks for the **asciminib 40 mg QD add-on**, **asciminib 60 mg QD add-on**, **imatinib**, and **nilotinib** arms, respectively), more patients in the **asciminib add-on** arms remained on treatment at data cutoff
- In this population of patients who had been tolerating imatinib ≥1 year prior to study entry, **asciminib add-on** resulted in a slightly higher rate of AEs vs continued **imatinib**, although fewer than switching to **nilotinib**
- Serious AEs and AEs leading to treatment discontinuation occurred more frequently in the **nilotinib** arm vs the **asciminib add-on arms**

AE, adverse event.

<sup>a</sup> One patient in the continued imatinib arm was not treated due to patient decision. <sup>b</sup> AEs leading to dose adjustments/interruptions in ≥2 patients were neutropenia (n=2) in the asciminib 40 mg add-on arm and Gilbert syndrome and abdominal pain upper (n=2 each) in the nilotinib arm.

# All Grade AEs Occurring in $\geq 15\%$ of Patients in Any Arm



- AEs experienced with **asciminib add-on** did not occur in a dose-dependent manner
- There were no new or worsening safety findings with **asciminib add-on** compared with previous studies of asciminib monotherapy<sup>7,8</sup>

# Summary

- **MF:** The treatment landscape for MF is evolving, now with 3 approved JAK inhibitors. More JAK inhibitors, novel agents, and combination strategies are on the way.
- **PV:** Ropeginterferon alpha 2b is a new treatment option for patients with low-risk PV, as well as other cytoreductive agents or clinical trial with hepcidin analog rusfertide.
- **CML:** There are 6 approved BCR/ABL-targeted agents for CML, and sequencing/combo approaches in those with suboptimal response continues to improve.

**Contact:** [krpettit@med.umich.edu](mailto:krpettit@med.umich.edu)