Fred Hutch
Cancer Center

Best of ASH 2022: Updates in the management of MPNs and CML

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Disclosures

- Pfizer: research funding, consulting
- Novartis: consulting
- Ascentage: consulting

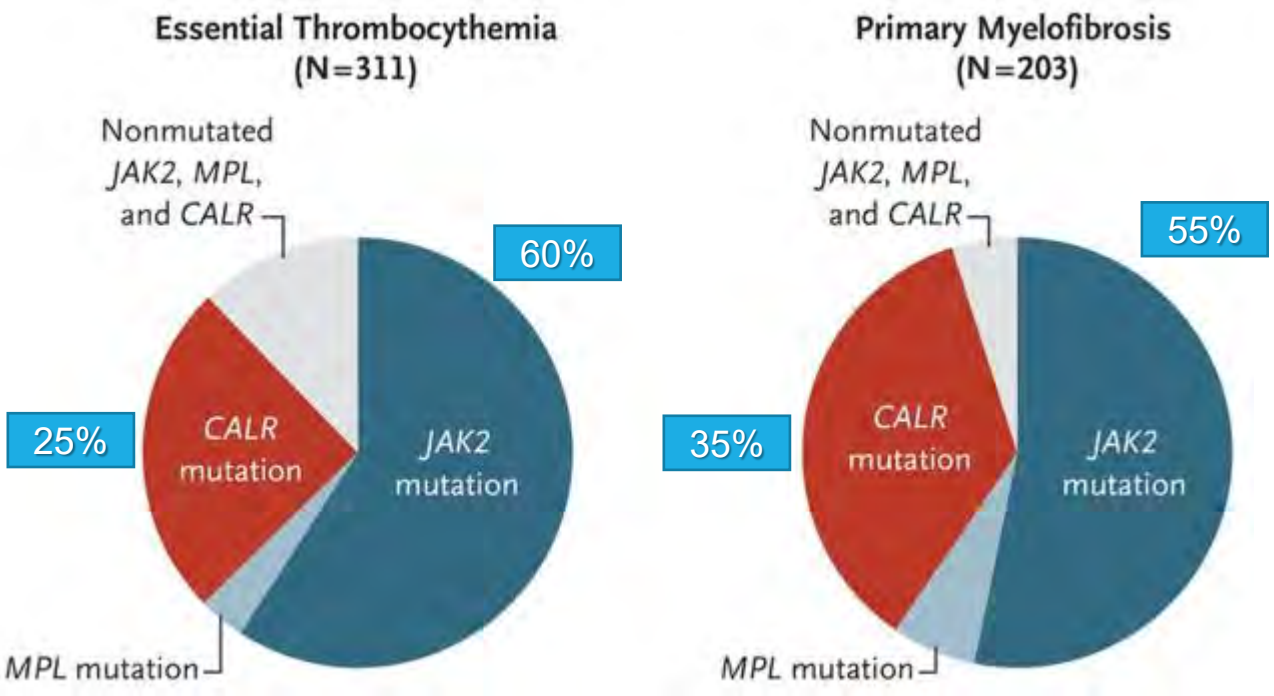
Learning objectives ASH 2022: Myeloproliferative Neoplasms

1. **Examining strategies to target Calreticulin (CALR) in MPNs**

2. **Approaches to individualizing JAK inhibitor therapy in myelofibrosis (MF) patients**

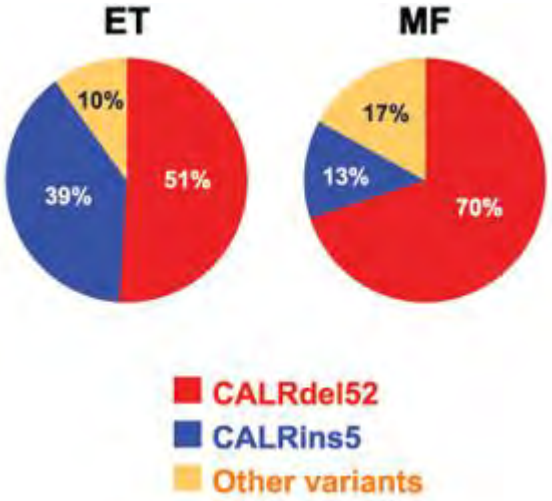
3. **Updates on novel therapeutics under evaluation in MF in later lines and frontline**

Calreticulin (*CALR*) mutations in ET and MF



CALR has chaperone and calcium buffering activities

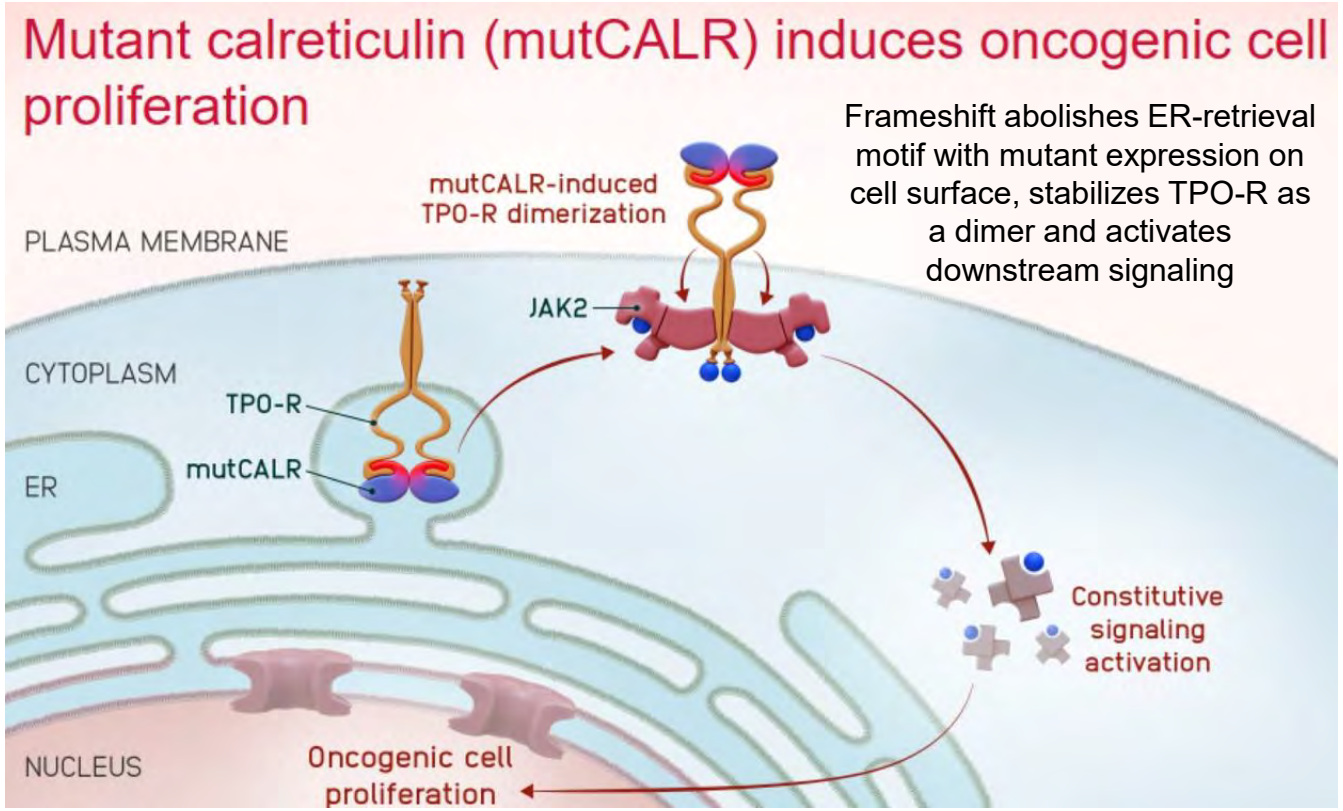
1. Examining strategies to target CALR in MPNs

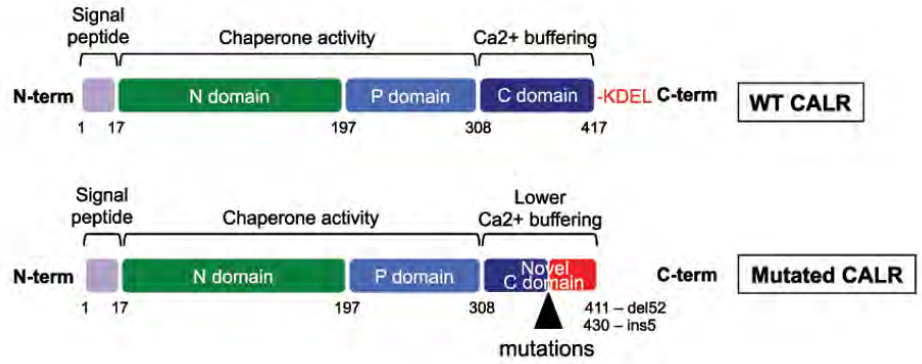


- Exon 9 somatic insertions or deletions
  - Type 1: 52 bp deletion
    - Most frequent
  - Type 2: 5 bp TTGTC insertion

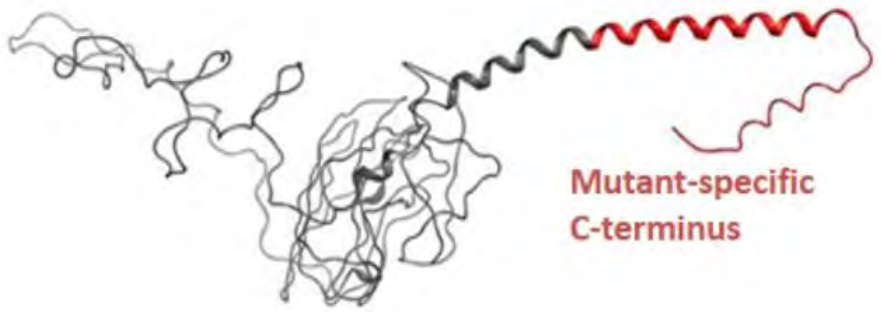
Klampf T et al. N Engl J Med 2013;369:2379-90.
Vainchenker W, Constantinescu SN and Plo I. F1000Research 2016, 5:700
Pietra D et al. Leukemia. 2016 Feb;30(2):431-8.

Targeting the mutant cell surface protein CALR





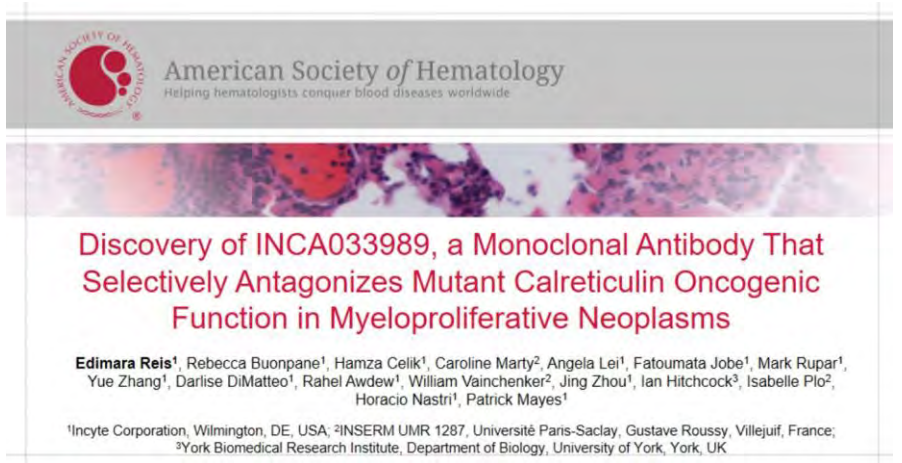
Loss of KDEL sequence and altered C-terminus



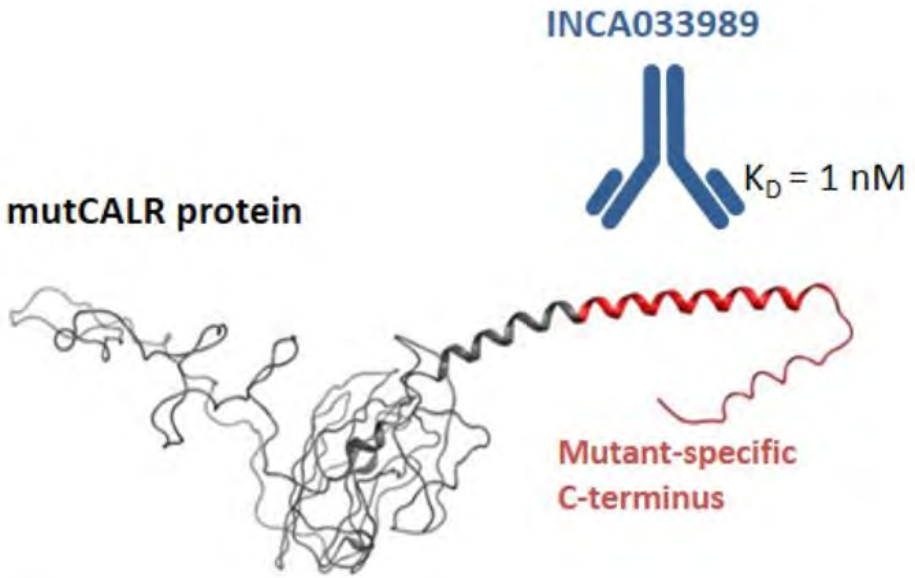
Vainchenker W, Constantinescu SN and Plo I. F1000Research 2016, 5:700

Reis E et al. Discovery of INCA033989, a Monoclonal Antibody That Selectively Antagonizes Mutant Calreticulin Oncogenic Function in Myeloproliferative Neoplasms (MPNs). Annual American Society of Hematology Meeting, December 2022. Oral abstract 6

INCA033989: a mutCALR-specific monoclonal antibody



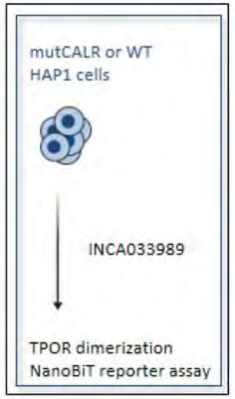
- Fully human IgG1
- Fc-silent
- Selective binding to mutCALR
- Antagonizes mutCALR-induced signaling and oncogenic function

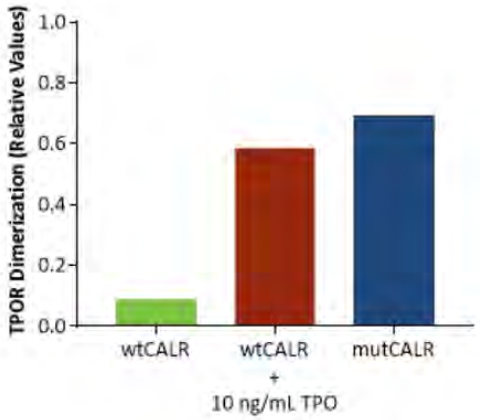


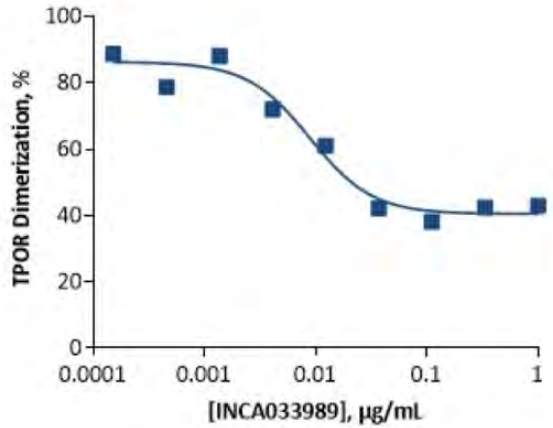
Structure generated with RaptorX (Toyota Technological Institute at Chicago, IL, USA).
IgG, immunoglobulin G; Fc, fragment crystallizable; K_D, equilibrium dissociation constant.

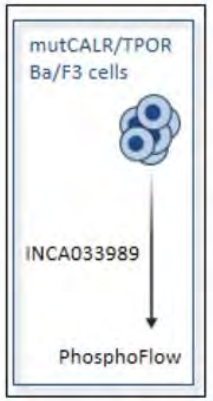
Reis E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 6

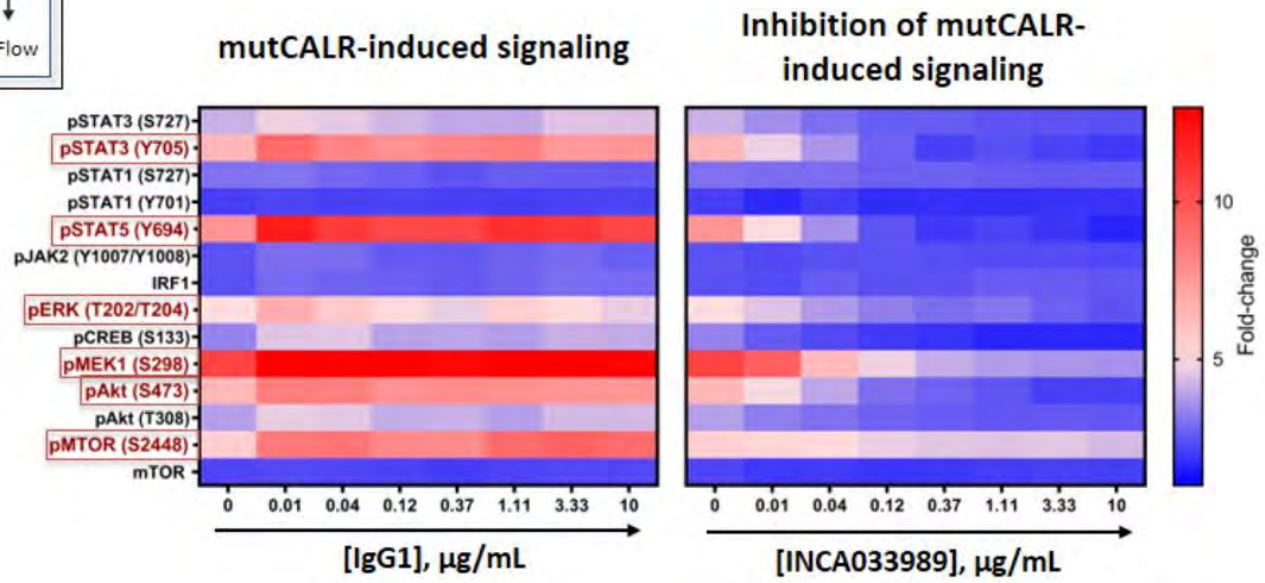
INCA033989 inhibits mutCALR-induced TPOR dimerization and oncogenic signaling in cell lines





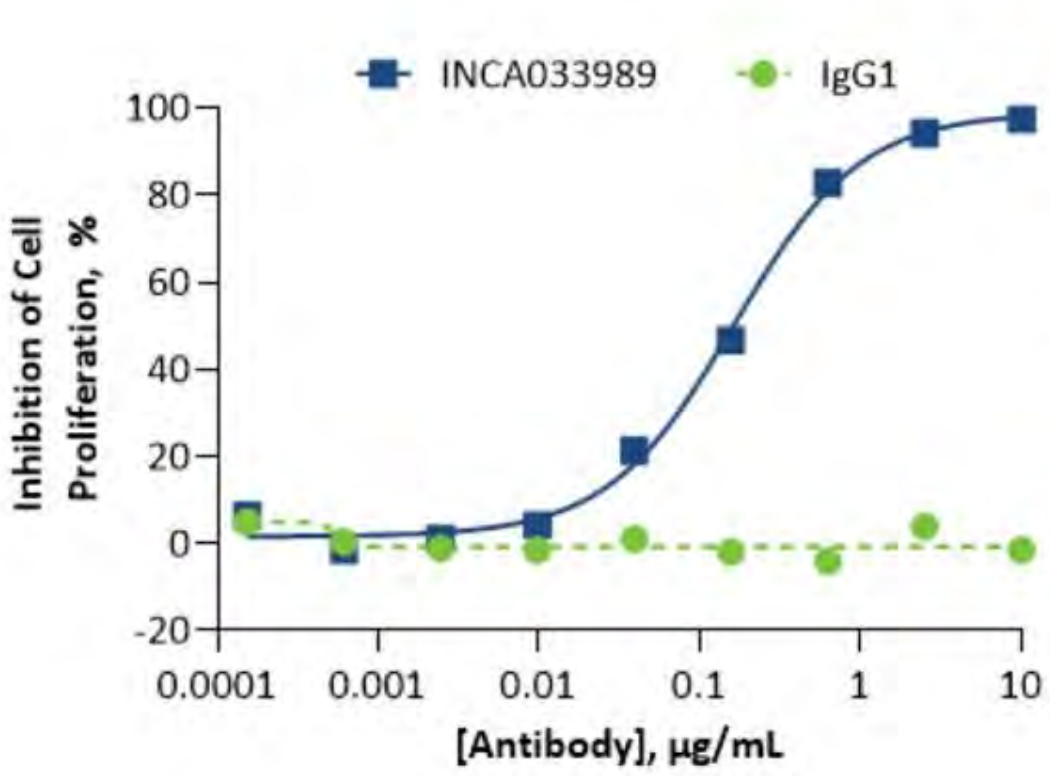


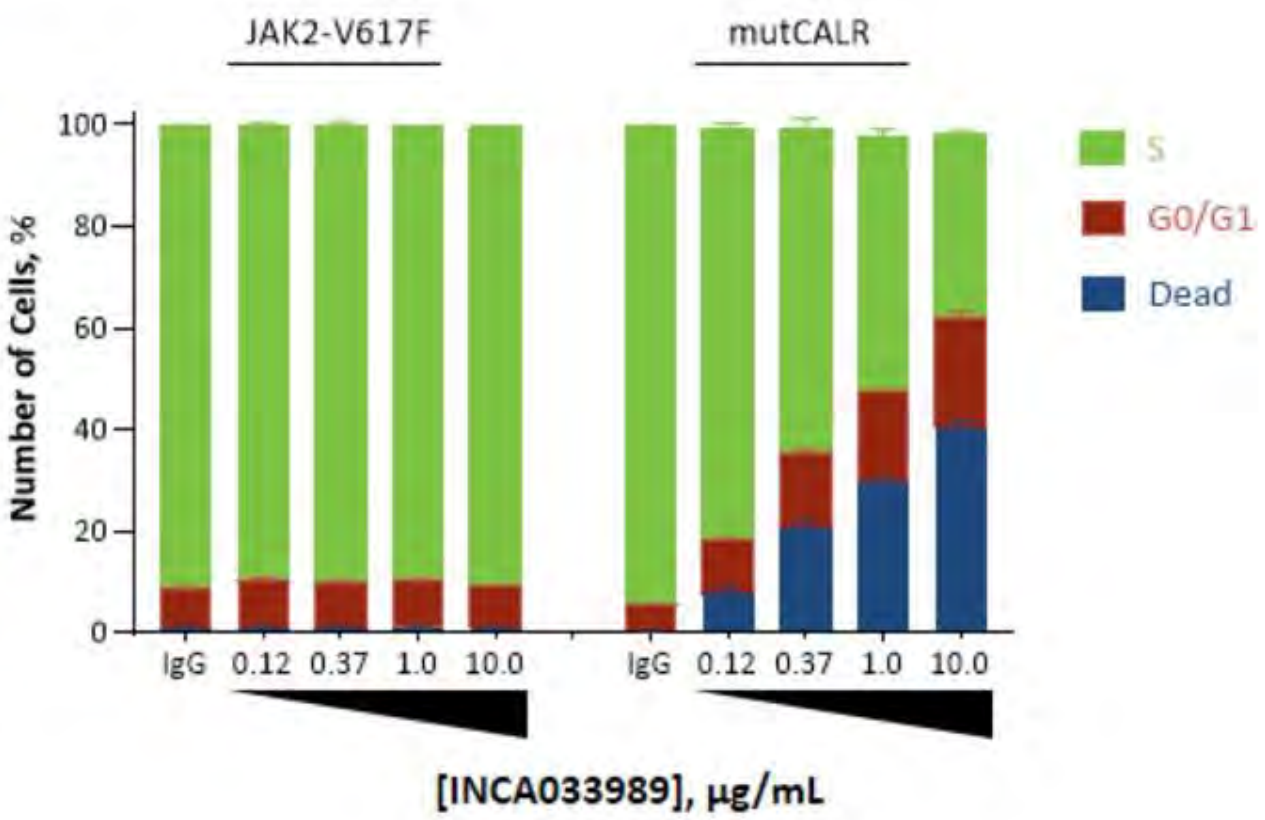




Reis E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 6

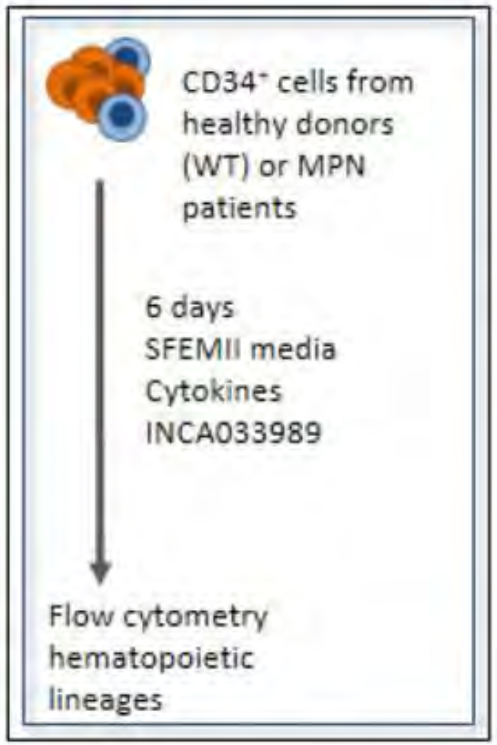
INCA0033989 selectively inhibits cell proliferation and induces death of mutCALR+ cells

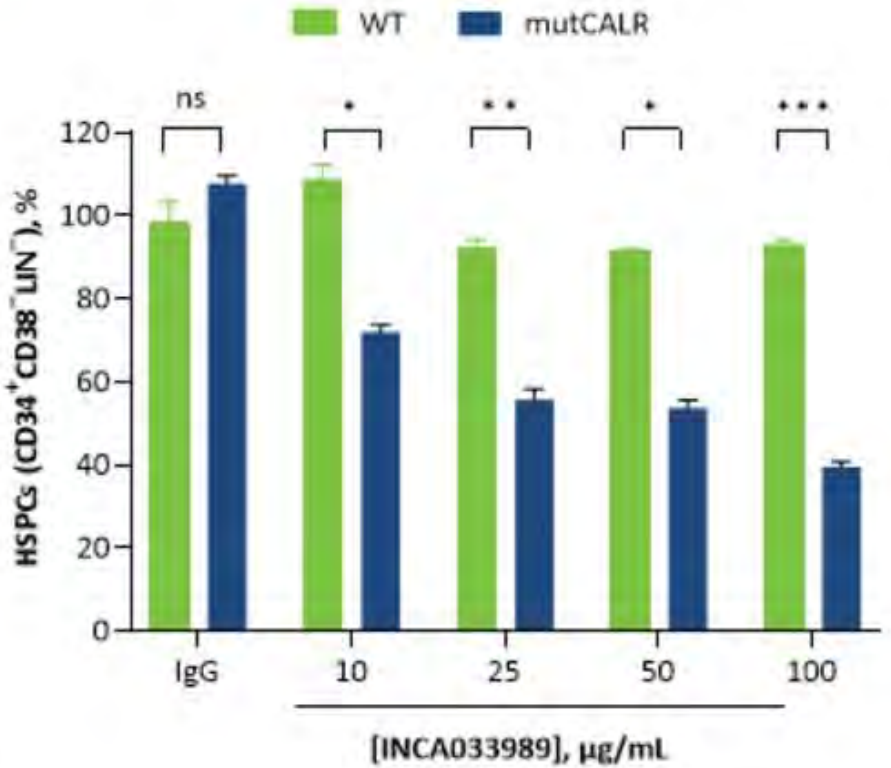


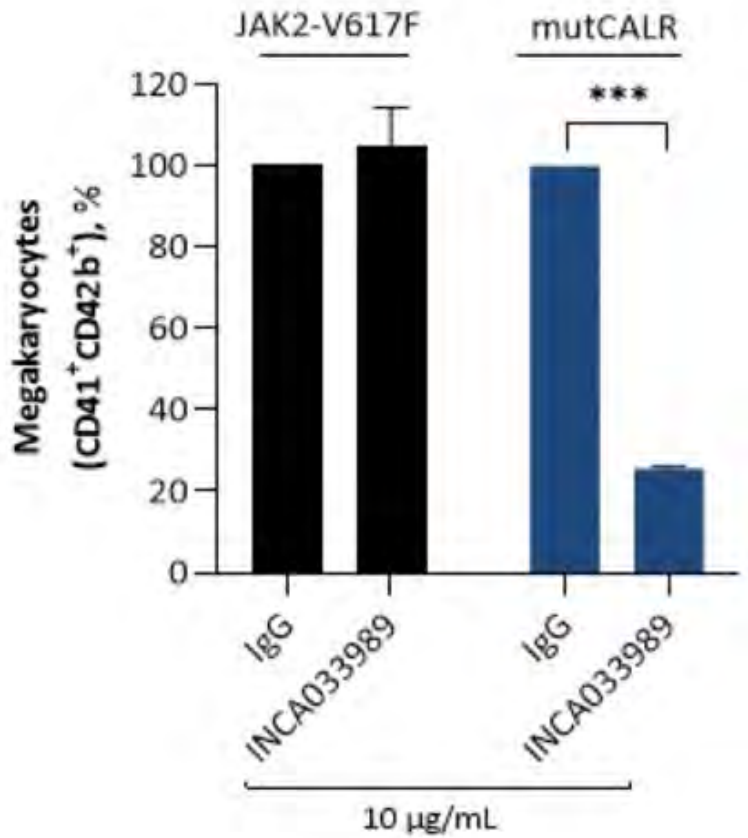


Reis E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 6

INCA033989 selectively inhibits the proliferation of mutCALR+ hematopoietic stem/progenitor cells



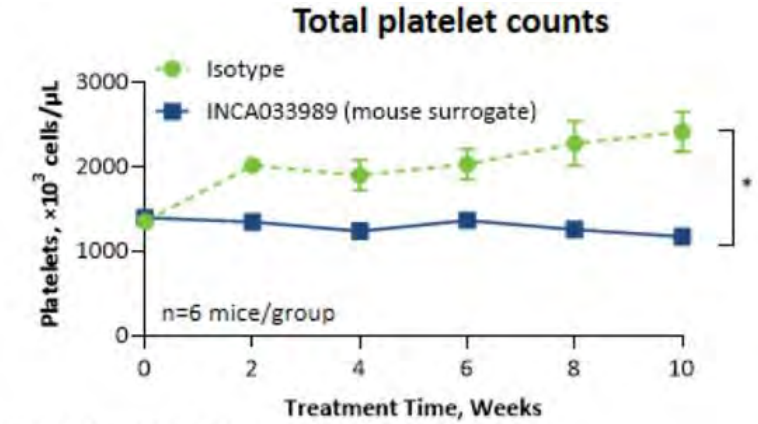




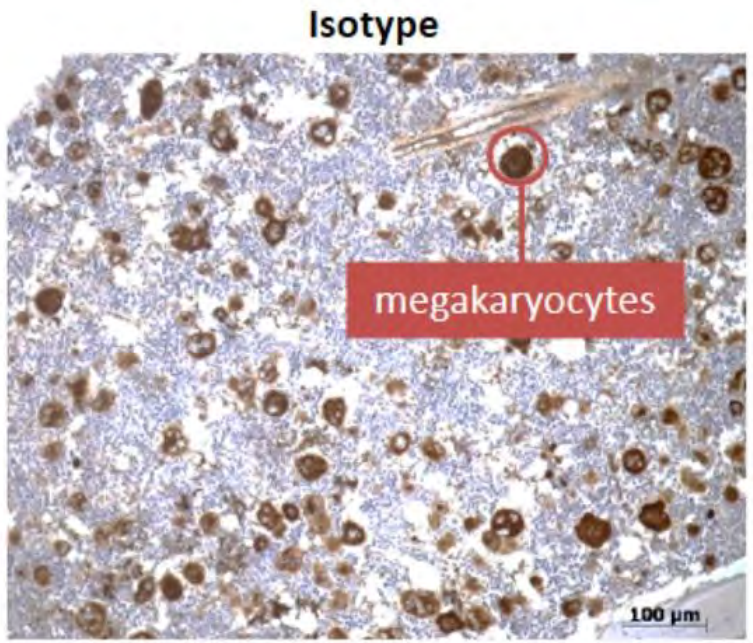
*P<0.01; **P<0.001; ***P<0.0001.
HSPC, hematopoietic stem progenitor cells; ns, not significant.

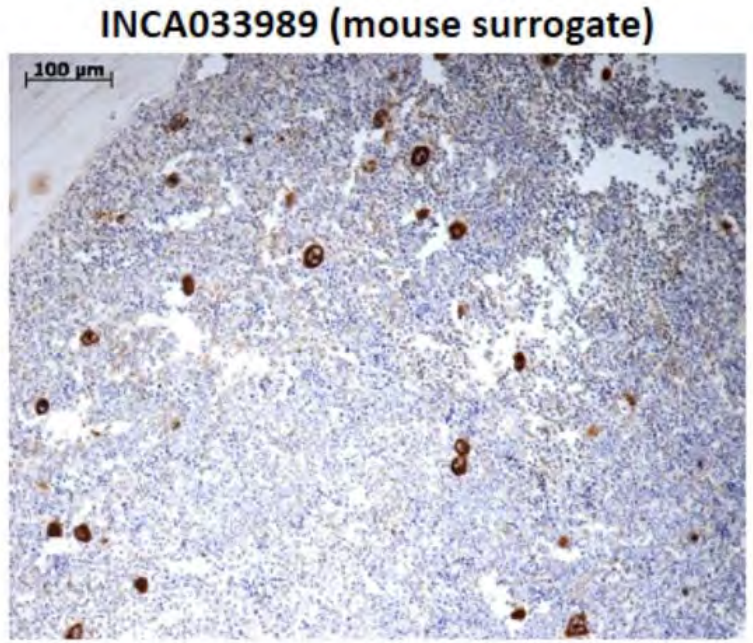
Reis E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 6

INCA033989 reduces platelets and re-establishes normal megakaryopoiesis in a mouse model of ET



*P<0.001; **P<0.0001.





Megakaryocytes stained with anti–von Willebrand factor antibody.

Reis E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 6

Conclusions

1. INCA033989 is a potent antagonist of mutant calreticulin function
   - Selective inhibition of JAK/STAT signaling and proliferation of *CALR*-mutated stem/progenitor cells
   - Potential to alter the course of disease in ET and MF patients by targeting disease-initiating (stem) cells

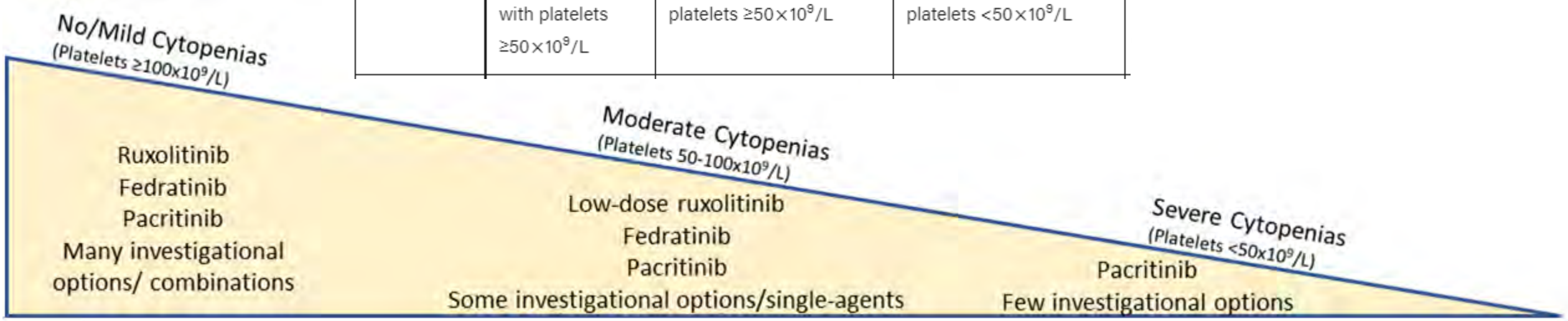
2. Provide a strong rationale for the clinical investigation of INCA033989 in MF and ET patients with *CALR* mutations and a Phase 1 study of INCA033989 is planned in 2023

Reis E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 6

FDA approved JAK inhibitors for myelofibrosis (MF) patients: the difficulties of managing cytopenic MF

Jak inhibitor	Approved agents		
	Ruxolitinib	**Fedratinib**	**Pacritinib**
Targets	Jak1, Jak2	Jak2, Jak1, FLT3, BRD4, TYK2, many others	Jak2, IRAK1, FLT3
Indications	Symptomatic MF with platelets $\geq 50 \times 10^9$/L	Symptomatic MF with platelets $\geq 50 \times 10^9$/L	Symptomatic MF with platelets $< 50 \times 10^9$/L

2. Approaches to individualizing JAK inhibitor therapy in myelofibrosis (MF) patients



Samuel B. Reynolds, Kristen Pettit; New approaches to tackle cytopenic myelofibrosis. Hematology Am Soc Hematol Educ Program 2022; 2022 (1): 235–244

Anemia in myelofibrosis and ruxolitinib-treated patients

1. Hemoglobin level of below sex-adjusted lower limit of normal present in 86% of the patients
   - Moderate (Hgb ≥ 8 and <10 g/dl) in 14%
   - Severe (Hgb < 8 g/dl or transfusion-dependent) in 37%
   - Due to disease-related inflammation, marrow fibrosis, splenic sequestration, and drug-induced
   - Many progress to transfusion dependence

Survey of 1109 consecutive PMF patients

	COMFORT-I		COMFORT-II	
Event, % of patients	Ruxolitinib (n=155)	Placebo (n=151)	Ruxolitinib (n=146)	BAT (n=73)
Anemia				
All grades	96.1	86.8	96	94
Grade ≥ 3	45.2	19.2	42	31

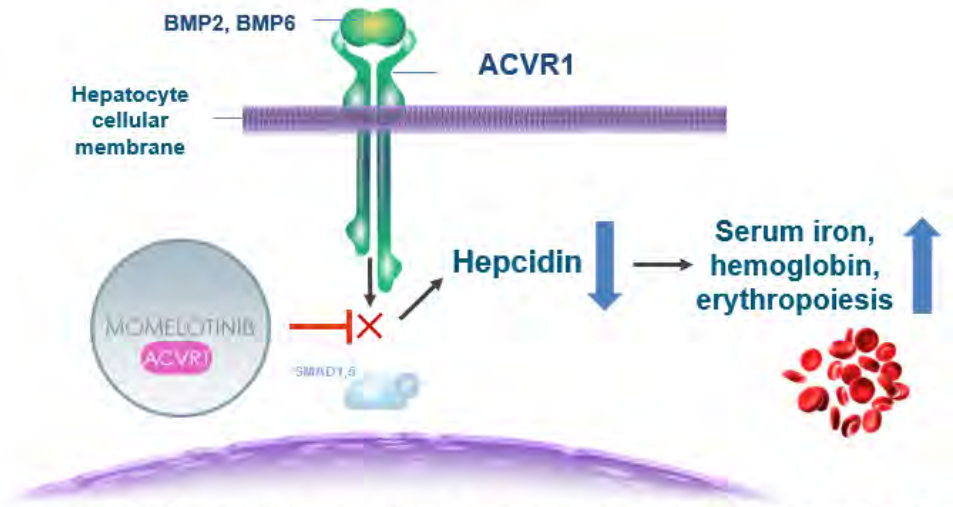
2. 60% of ruxolitinib-treated patients in COMFORT-I received RBC transfusions during randomized treatment and grade 3 or higher anemia was seen in 45.2% of ruxolitinib-treated patients vs. 19.2% in placebo-treated patients

Nicolosi M et al . Leukemia (2018) 32:1254–1258
Yi CA et al. Future Oncol. 2015 ; 11(5): 719–733.
Verstovsek S et al. N Engl J Med 2012; 366:799-807

Background: Momelotinib

Momelotinib (MMB) is a JAK1, JAK2 and ACVR1 inhibitor

- **Prior Ph3 studies: SIMPLIFY-1 and SIMPLIFY-2**
  - In JAK inhibitor naïve (S1) and JAK inhibitor treated (S2) patient populations
- **Previously reported data suggest that momelotinib:**
  - Provides similar splenic response for momelotinib vs ruxolitinib
  - Improves constitutional symptoms
  - Reduces transfusion burden and improves anemia
  - Has a favorable safety profile



Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF[1]. **ACVR1** inhibition decreases hepcidin production, restores iron homeostasis, and promotes erythropoiesis

SIMPLIFY-1	Safety Population (Randomized Period) MMB (N=214)	RUX (N=216)
Thrombocytopenia Grade 3/4	15 (7.0%)	10 (4.6%)
[2]Anemia Grade 3/4	**13 (6.1%)**	**49 (22.7%)**

[1]Oh S et al. Blood Adv (2020) 4 (18): 4282–4291.
[2]Verstovsek S et al. ASH Annual Meeting Abstracts. 2020. Abstract 54.
Gerds AT et al. Updated results from the Momentum Phase 3 study of momelotinib vs danazol in symptomatic and anemic myelofibrosis Annual American Society of Hematology Meeting, December 2022. Oral abstract 627.

MOMENTUM is an Ongoing Phase 3 Study of Momelotinib Versus Danazol in Symptomatic, Anemic, JAKi-Experienced Patients

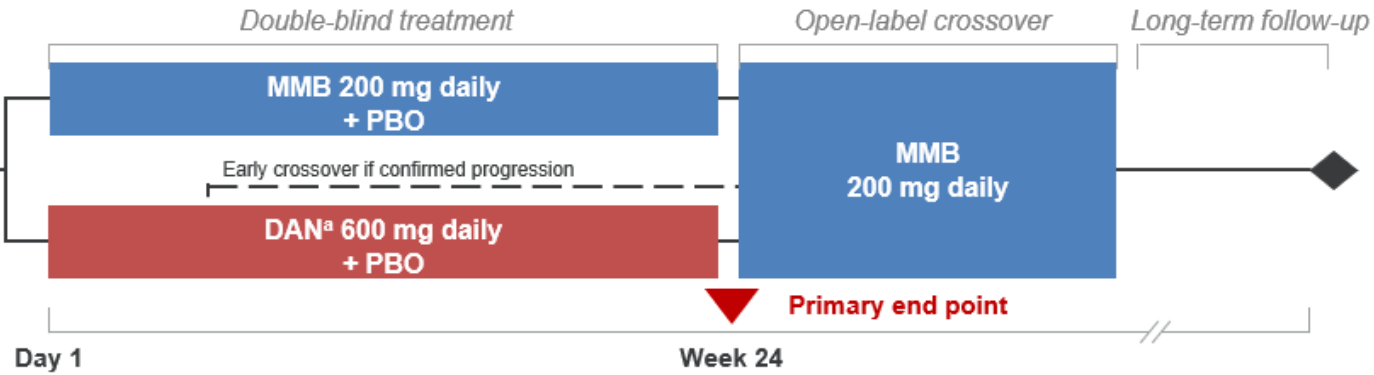
Previously treated with JAKi
Symptomatic (TSS ≥10)
Anemic (Hgb <10 g/dL)
Platelets ≥25×10⁹/L

Stratification:
- TSS
- Palpable spleen length
- Transfused units in prior 8 weeks
- Study site

Patients
N=195

2:1 randomization
JAKi taper/washout ≥21 days

Planned enrollment: 180
FPE Apr 2020
LPE Jun 2021
Database lock Dec 2021




American Society of Hematology
Helping hematologists conquer blood diseases worldwide

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

Presentation 627 | Presented at the 64th American Society of Hematology Annual Meeting & Exposition, New Orleans, LA, USA | December 10-13, 2022

MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met[1,2]

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

1. Mesa R, et al. Abstract presented at: 2022 ASCO Annual Meeting; June 3-6, 2022; Chicago, IL and Virtual. Abstract 7002. 2. Verstovsek S, et al. Abstract presented at: 2022 EHA Congress; June 9-12; 2022; Vienna, Austria and Virtual. Abstract S195. Gerds AT et al. Updated results from the Momentum Phase 3 study of momelotinib vs danazol in symptomatic and anemic myelofibrosis Annual American Society of Hematology Meeting, December 2022. Oral abstract 627.

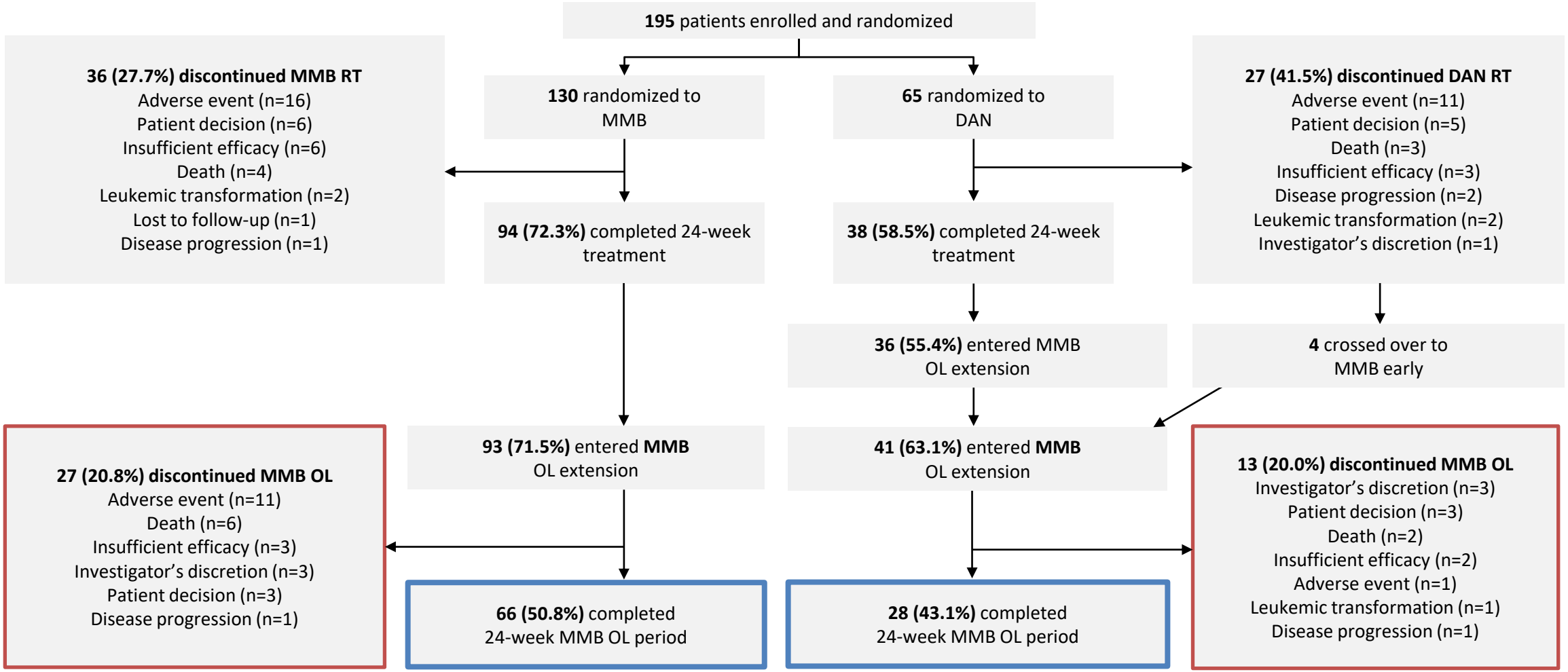
MOMENTUM Was Conducted in Symptomatic Anemic, Post-RUX Patients With MF and a Heavy Transfusion Burden

Baseline characteristics	MMB (N=130)	DAN (N=65)
Mean age, y	69.85	71.46
Male, %	60.8	67.7
PMF/PPV-MF/PET-MF, %	60.0/20.8/19.2	70.8/16.9/12.3
DIPSS Int-1/Int-2/High, %	5.4/55.4/38.5	4.6/61.5/29.2
Mean prior JAKi therapy, y	2.7	2.4
Mean Hgb, g/dL	8.1	7.9
Hgb <8 g/dL, %	47.7	49.2
TI,[a] %	13.1	15.4
TR,[b] %	38.5	32.3
TD,[c] %	48.5	52.3
Mean platelets, $\times 10^9$/L	151.7	130.7

[a]TI defined as not requiring RBC transfusion for ≥12 weeks, with Hgb levels ≥8 g/dL. [b]TR defined as patients who required transfusions but did not meet the criteria for TD. [c]TD defined as requiring RBC transfusion ≥4 units in the 8 weeks before randomization.
DAN, danazol; DIPSS; Dynamic International Prognostic Scoring System; Hgb, hemoglobin; Int, intermediate; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MMB, momelotinib; PET, post-essential thrombocythemia; PMF, primary myelofibrosis; PPV, post-polycythemia vera; RBC, red blood cell; RUX, ruxolitinib; TD, transfusion dependence; TI, transfusion independence; TR, transfusion-requiring.

Gerds AT et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 627.

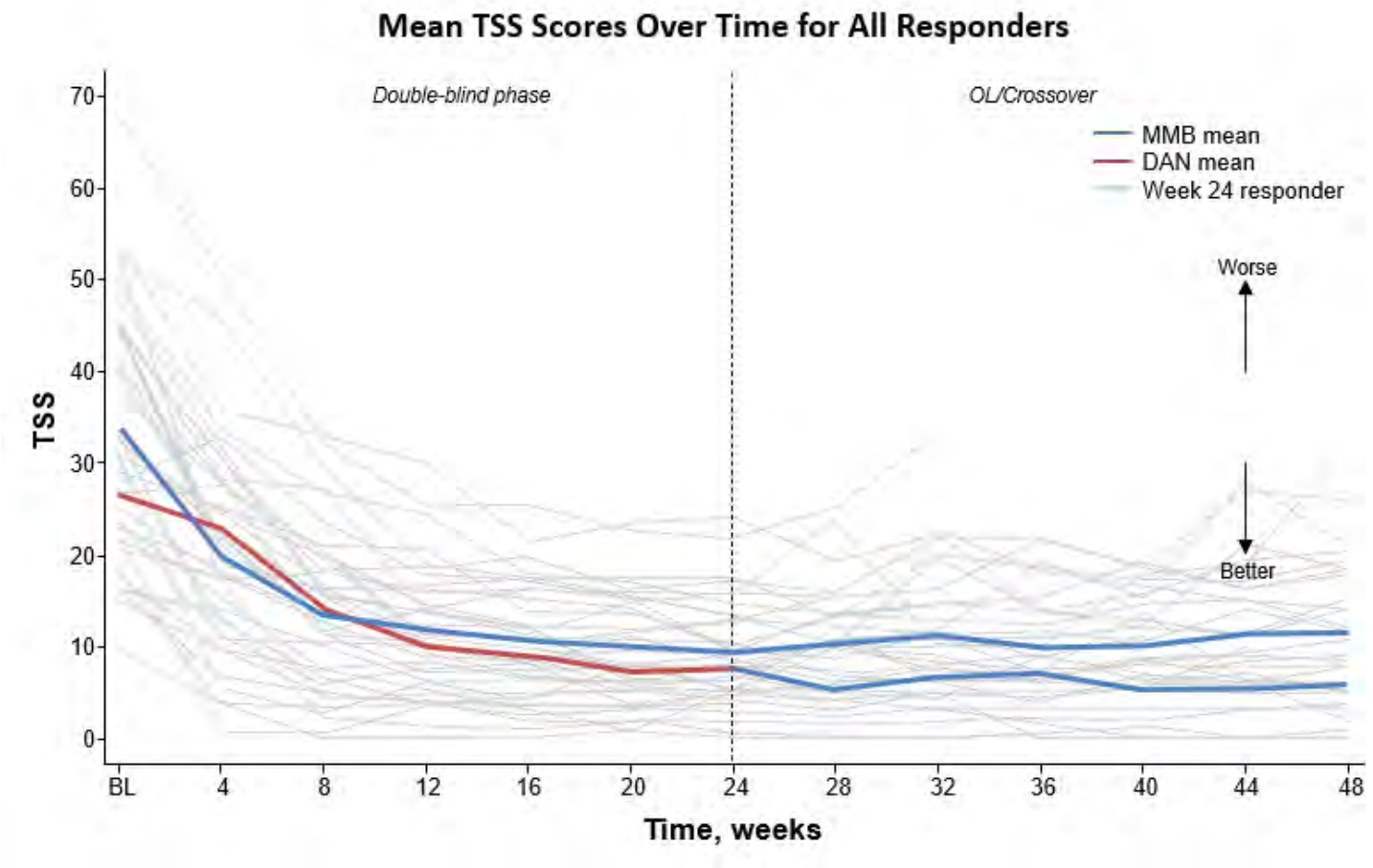
Patient Disposition: Data Cutoff May 17, 2022



DAN, danazol; MMB, momelotinib; OL, open-label; RT, randomized treatment.

Gerds AT et al. Updated results from the Momentum Phase 3 study of momelotinib vs danazol in symptomatic and anemic myelofibrosis Annual American Society of Hematology Meeting, December 2022. Oral abstract 627.

Week 24 Symptom Responses[a] Were Sustained Through Week 48



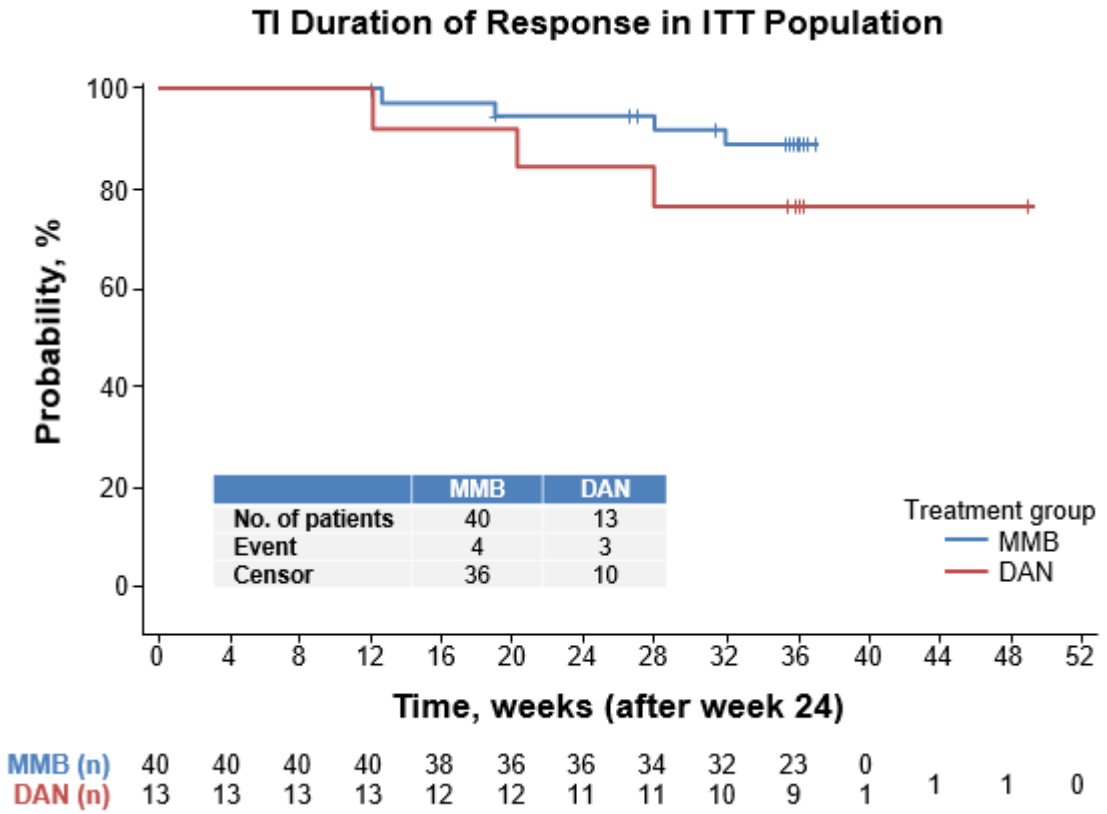
- Week 24 TSS response was 25% in the MMB group and 9% in the DAN group
- Week 24 TSS response was maintained in 31 of 32 (97%) MMB→MMB and 6 of 6 (100%) DAN→MMB patients

ADDITIONALLY,

- 10 of 35 (29%) DAN → MMB week 24 TSS nonresponders were new responders at week 48
- 12 of 61 (20%) MMB → MMB week 24 TSS nonresponders were also new responders at week 48

[a]Defined as the proportion of patients who achieve ≥50% reduction in TSS over the 28 days immediately before the end of week 24 compared with baseline.
DAN, danazol; MMB, momelotinib; OL, open-label; TSS, total symptom score.
Gerds AT et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 627.

Week 24 TI Responses[a] Were Sustained Through Week 48

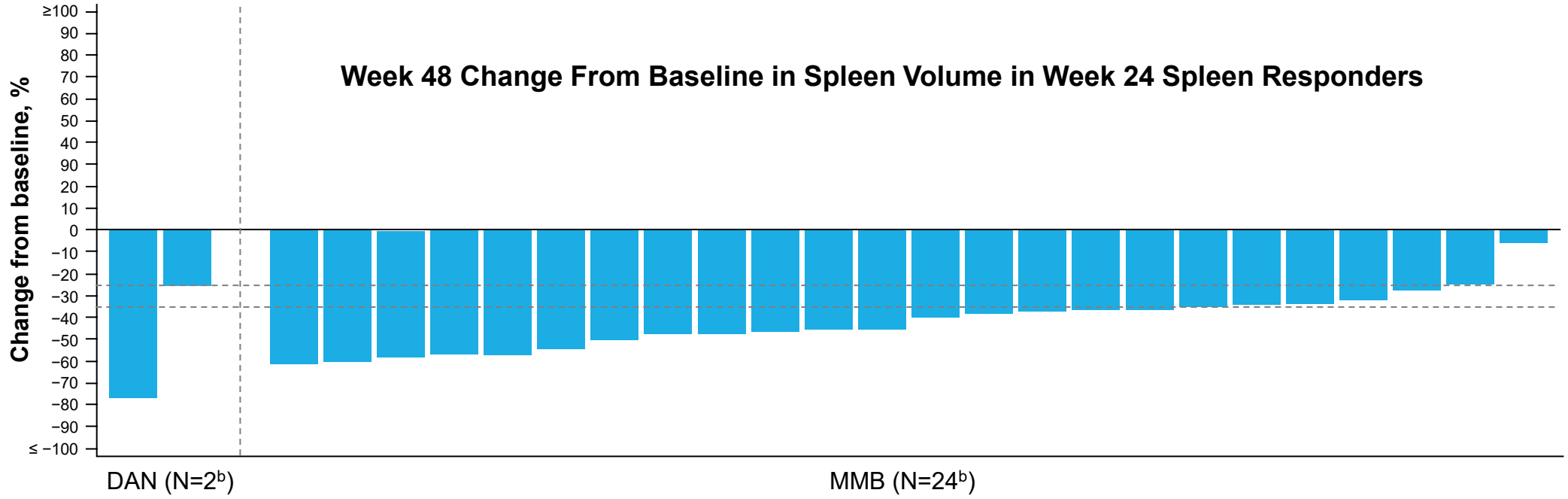


- Week 24 TI response was 31% in the MMB group and 20% in the DAN group
  - Consecutive 12-week TI-R[b] was 44.6% in the MMB group and 29.2% in the DAN group (Poster #3028)
- **Week 24 TI response was maintained in 36 of 40 (90%) MMB→MMB and 10 of 13 (77%) DAN→MMB patients**

[a]Defined as not requiring RBC transfusion in the prior 12 weeks and Hgb levels ≥8 g/dL; [b]Consecutive 12-week TI-R (defined as absence of RBC transfusions and no Hgb measurement below 8 g/dL over any 12-week period through week 24)
BL, baseline; DAN, danazol; Hgb, hemoglobin; ITT, intention-to-treat; MMB, momelotinib; OL, open-label; RBC, red blood cell; RT, randomized treatment; TI, transfusion independence.

Gerds AT et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 627.

Week 24 Spleen Responses[a] Were Sustained Through Week 48



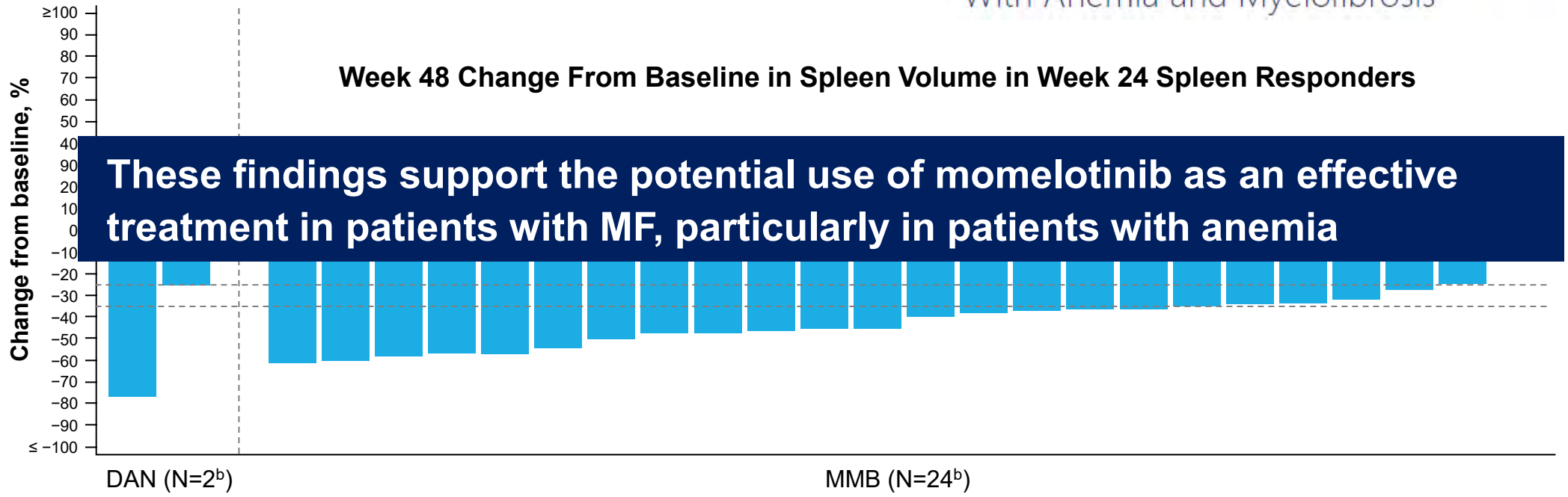
- Week 24 SRR35 response was 23% in the MMB group and 3% in the DAN group
- **All SRR35 responders at week 24 maintained spleen volume below baseline (24 of 24 MMB→MMB and 2 of 2 DAN→MMB patients)**

[a]Defined as the proportion of patients who have a reduction in spleen volume of ≥35% from baseline. [b]N is the number of patients with percent change in spleen volume at week 48 available.
DAN, danazol; MMB, momelotinib; SRR35, splenic response rate >35%.

Gerds AT et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 627.

Week 24 Spleen Responses[a] Were Sustained Through Week 48

FDA Accepts NDA for Momelotinib in Patients With Anemia and Myelofibrosis



These findings support the potential use of momelotinib as an effective treatment in patients with MF, particularly in patients with anemia

- Week 24 SRR35 response was 23% in the MMB group and 3% in the DAN group
- **All SRR35 responders at week 24 maintained spleen volume below baseline (24 of 24 MMB→MMB and 2 of 2 DAN→MMB patients)**

[a]Defined as the proportion of patients who have a reduction in spleen volume of ≥35% from baseline. [b]N is the number of patients with percent change in spleen volume at week 48 available. DAN, danazol; MMB, momelotinib; SRR35, splenic response rate >35%.

Gerds AT et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 627.

Pacritinib in MF patients

On February 28, 2022, the FDA approved pacritinib (Vonjo) for the treatment of adults with intermediate- or high-risk primary or secondary (post–polycythemia vera or post–essential thrombocythemia) myelofibrosis with a platelet count below 50 × 10^9/L.

- Accelerated approval based on **phase III PERSIST-2** study in patients with myelofibrosis (platelet counts ≤ 100 × 109/L).
    1. Patients were randomly assigned 1:1:1 to receive pacritinib at either 200 mg twice daily, 400 mg once daily, or best available therapy.
    2. Cohort of patients with baseline platelet counts below 50 × 109/L who were treated with pacritinib at 200 mg twice daily, 29% of patients had a reduction in spleen volume of at least 35% compared to 3% of patients receiving best available therapy, which included ruxolitinib.
    3. Ongoing phase 3 PACIFICA trial, with expected results in mid-2025.

Pacritinib in patients with anemia

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

Session 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Towards Personalized Medicine in Myeloproliferative Neoplasms and Mastocytosis: New and Repurposed Drugs for Unmet Clinical Needs

Dec 11, 2022, #628

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

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

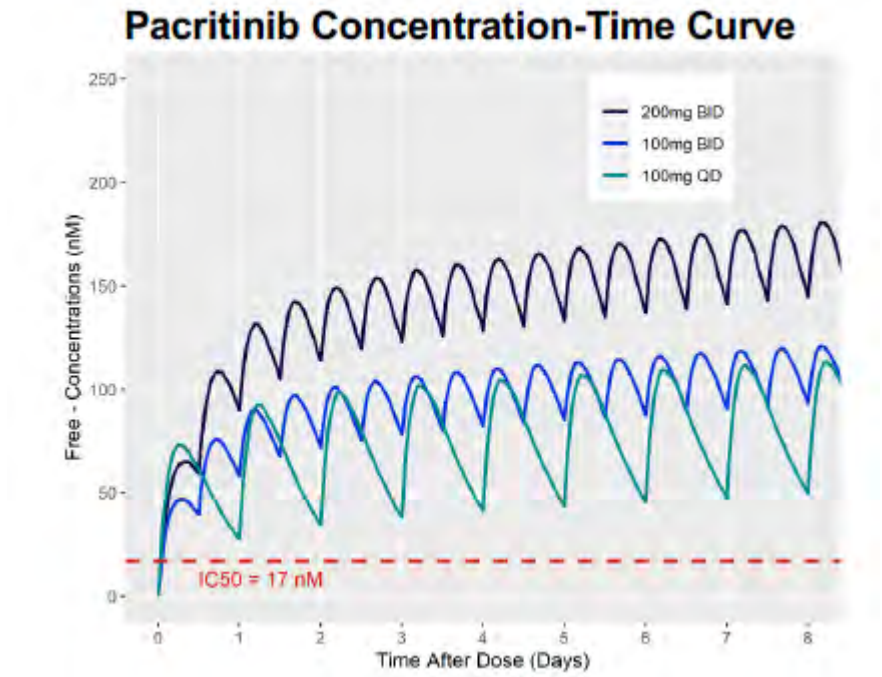
Pacritinib is a potent ACVR1 inhibitor

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

	+ Control LDN 193189[a]	PAC C_{max} 213 nM	MMB C_{max} 168 nM	FED C_{max} 275 nM	RUX C_{max} 47 nM
Replicate 1 ACVR1 IC_{50} (nM)	20.4	22.6	70.2	312.0	>1000
Replicate 2 ACVR1 IC_{50} (nM)	32.4	10.8	34.9	235.0	>1000
Mean ACVR1 IC_{50} (nM)	26.4	16.7	52.6	273.5	>1000
Potency[b] (C_{max}:IC_{50})	N/A	12.7	3.2	1.0	<0.01

[a]LDN 193189 is an ACVR1 inhibitor.
[b]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.

Legend
Higher potency
Lower potency



- Assessed potency of JAKi against ACVR1 by *in vitro* HotSpot assay to calculate IC50 and potency (ratio of clinical Cmax:IC50)
- Modeled concentration-time curves of free drug using R
- Pacritinib decreased hepcidin expression *in vitro*

Oh ST et al. Pacritinib is a potent ACVR1 inhibitor with significant anemia benefit in patients with myelofibrosis. Annual American Society of Hematology Meeting, December 2022. Oral abstract 628.

Methods: analysis of transfusion independence

- Evaluated pacritinib 200 mg BID dose (approved dose) vs. best available treatment (BAT) on PERSIST-2 focusing on patients who were not TI at baseline and who were randomized ≥12 weeks prior to study termination
  - BAT: 42% ruxolitinib (5 mg daily, median dose), 26% (danazol, ESAs, IMiDs, steroids), 19% watch and wait

Oh ST et al. Pacritinib is a potent ACVR1 inhibitor with significant anemia benefit in patients with myelofibrosis. Annual American Society of Hematology Meeting, December 2022. Oral abstract 628.

More pacritinib patients achieved transfusion independence and transfusion reduction through week 24

- TI (Gale criteria): no RBC transfusion over 12 weeks
- TI (SIMPLIFY criteria): no RBC transfusion & no hemoglobin <8 g/dL over 12 weeks

TI Conversion Rate

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

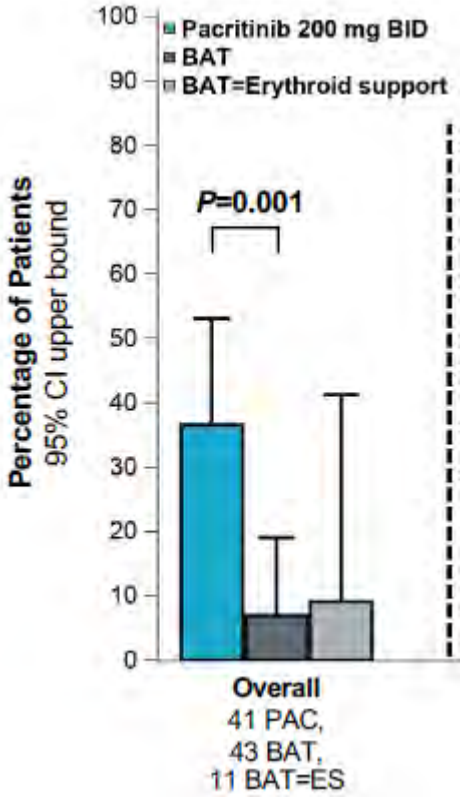
- Erythroid support agents were prohibited on the pacritinib arm

TI Conversion Rate

Pacritinib N=42	BAT N=44	*P*-value
24%	5%	0.013

- Similar results based on SIMPLIFY criteria for TI

Gale criteria

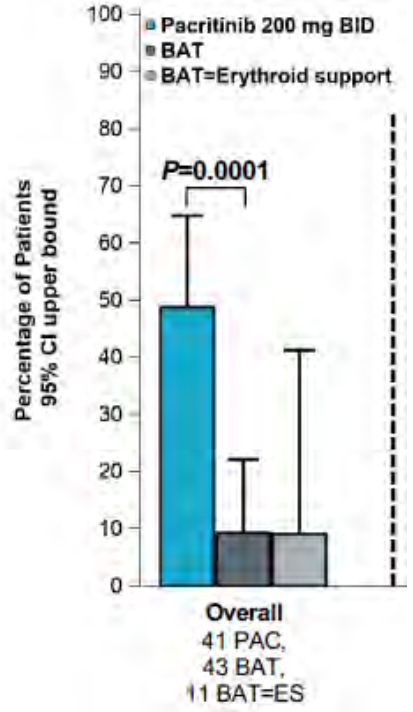


Transfusion Reduction

Pacritinib N=41	BAT N=43	*P*-value
49%	9%	0.0001

Rate of ≥50% Transfusion Reduction

Over 12-week interval through week 24



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These findings support the potential use of pacritinib as an effective treatment in patients with anemia in MF, as well as thrombocytopenia

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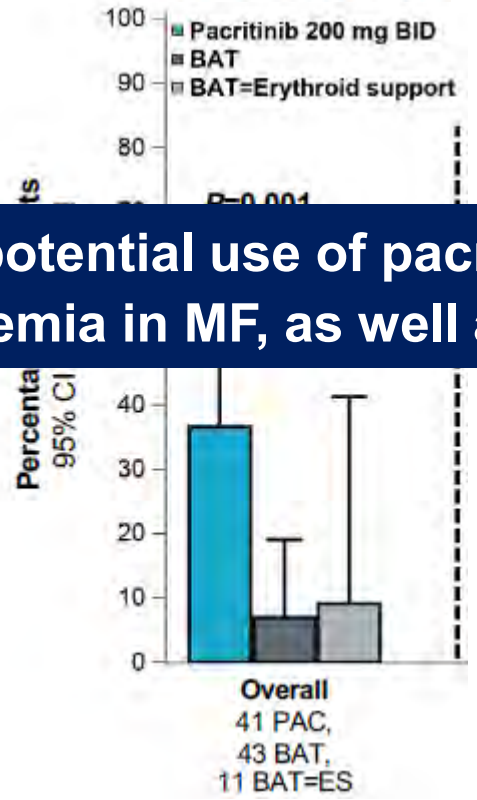

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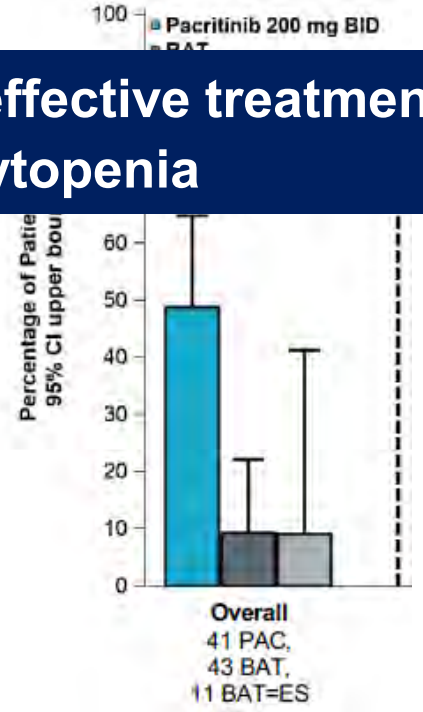
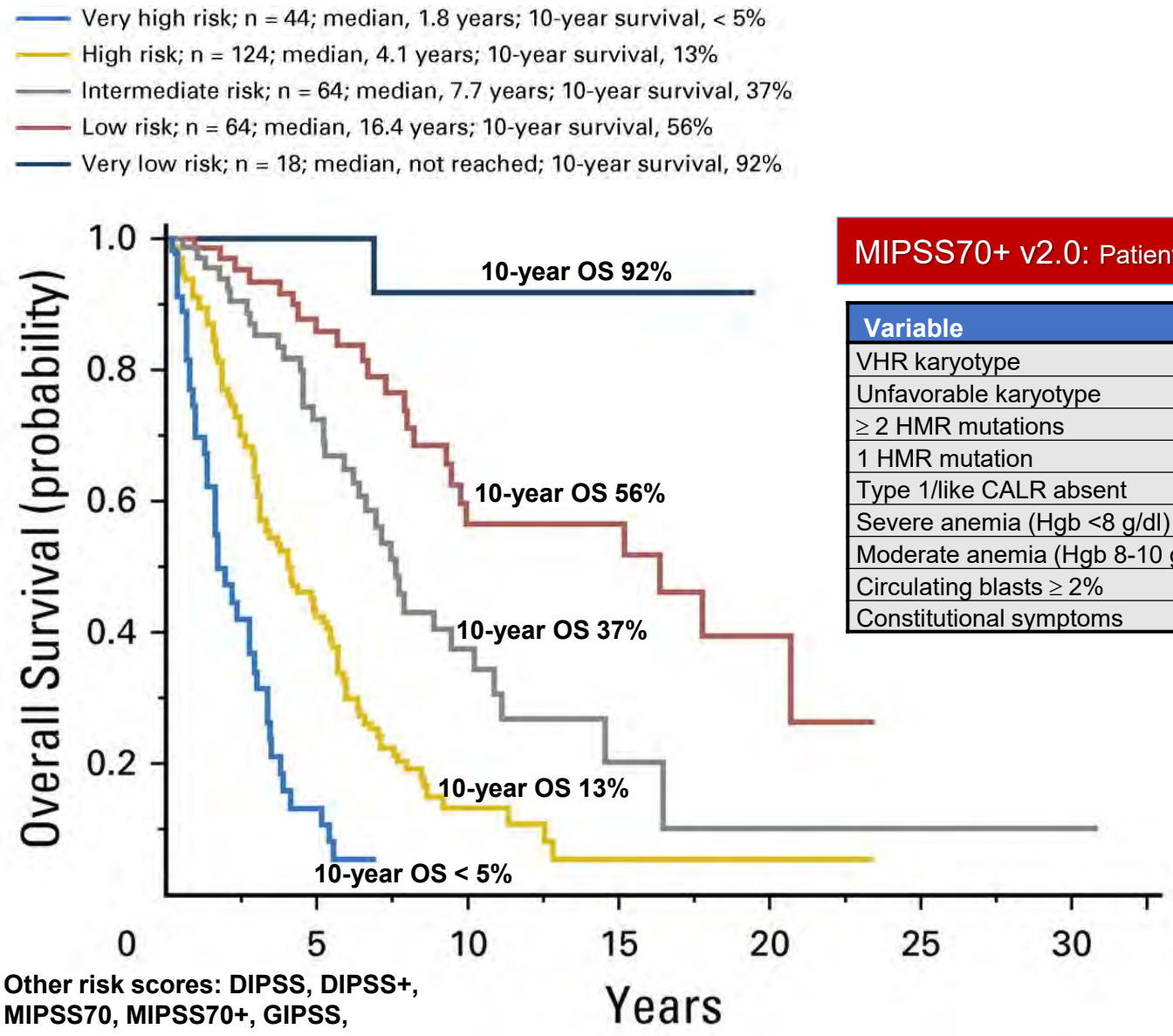


Oh ST et al. Pacritinib is a potent ACVR1 inhibitor with significant anemia benefit in patients with myelofibrosis. Annual American Society of Hematology Meeting, December 2022. Oral abstract 628.

MF patient outcomes



Other risk scores: DIPSS, DIPSS+, MIPSS70, MIPSS70+, GIPSS, MYSEC-PM (secondary MF), MTSS (SCT)

3. Updates on novel therapeutics under evaluation in MF in later lines and frontline

MIPSS70+ v2.0: Patients ≤ 70 years

Variable	Points
VHR karyotype	4
Unfavorable karyotype	3
≥ 2 HMR mutations	3
1 HMR mutation	2
Type 1/like CALR absent	2
Severe anemia (Hgb <8 g/dl)	2
Moderate anemia (Hgb 8-10 g/dl)	1
Circulating blasts ≥ 2%	1
Constitutional symptoms	2

HMR : presence of a mutation in *ASXL1, SRSF2, EZH2, IDH1, IDH2, or U2AF1Q157*

Unfavorable Karyotype: Any karyotype other than very high-risk karyotype, normal karyotype, or sole abnormalities of 20q-, 13q-, 19, chromosome 1 translocation/duplication, -Y, or sex chromosome abnormality other than –Y

Very-High-Risk Karyotype: Single or multiple abnormalities of -7, i(17q), inv(3)/3q21, 12p-/12p11.2, 11q-/11q23, or other autosomal trisomies not including 18/19

Tefferi A et al. J Clin Oncol. 2018 Jun 10;36(17):1769-1770

Novel therapeutic updates at ASH 2022

240 Preliminary Data from the Phase I/II Study of TP-3654, a Selective Oral PIM1 Kinase Inhibitor, in Patients with Myelofibrosis Previously Treated with or Ineligible for JAK Inhibitor Therapy

3037 MYF3001: A Randomized Open Label, Phase 3 Study to Evaluate Imetelstat Versus Best Available Therapy in Patients with Intermediate-2 or High-Risk Myelofibrosis Relapsed/Refractory to Janus Kinase Inhibitor

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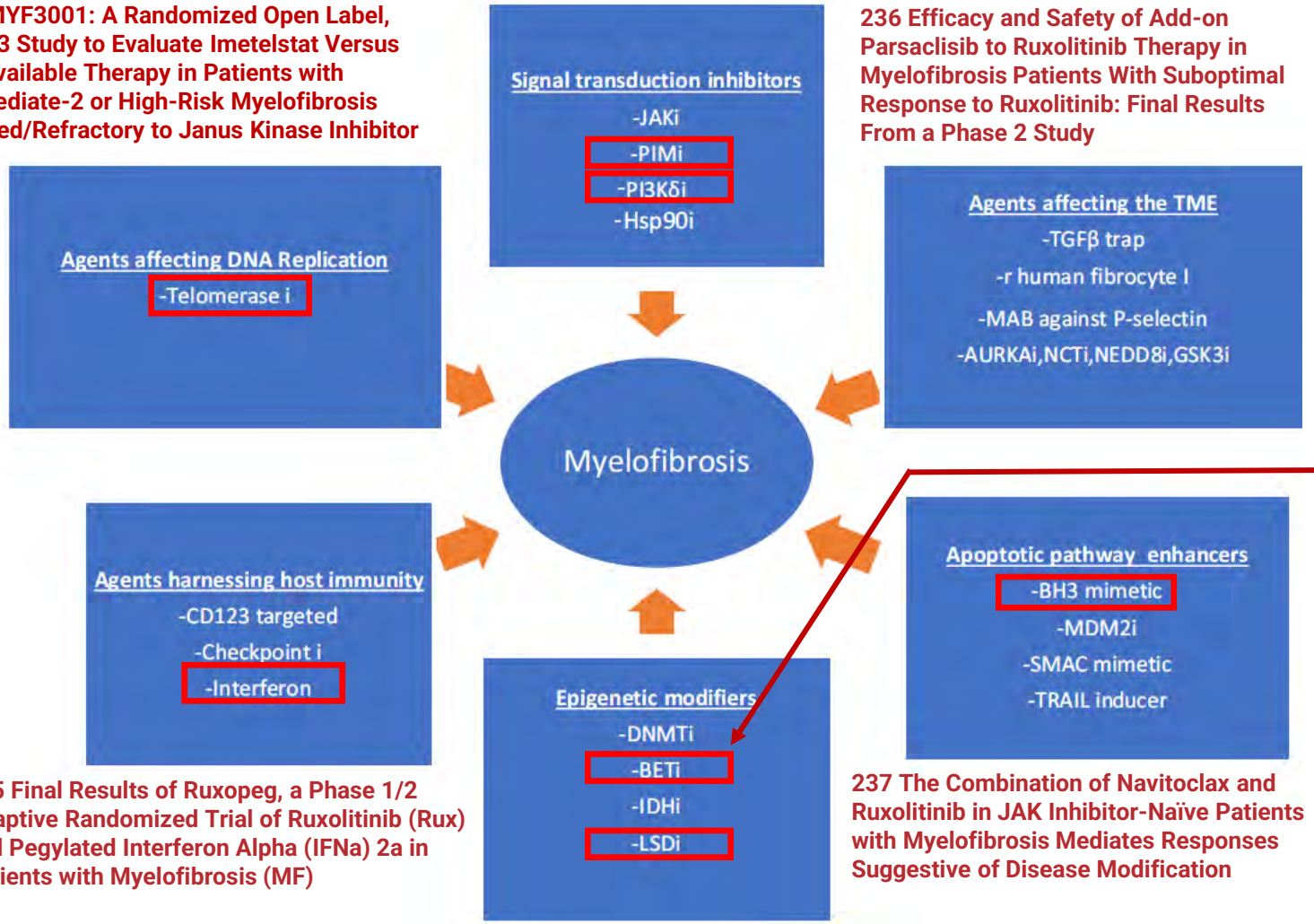

238 Pelabresib (CPI-0610) Combined with Ruxolitinib for JAK Inhibitor Treatment-Naïve Patients with Myelofibrosis: Durability of Response and Safety Beyond Week 24

235 Final Results of Ruxopeg, a Phase 1/2 Adaptive Randomized Trial of Ruxolitinib (Rux) and Pegylated Interferon Alpha (IFNa) 2a in Patients with Myelofibrosis (MF)

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

4368 A Phase 2 Study of the LSD1 Inhibitor Bomedemstat (IMG-7289) for the Treatment of Advanced Myelofibrosis (MF): Updated Results and Genomic Analyses

Adapted from Venugopal S and Mascarenhas. J Hematol Oncol. 2020 Dec 2;13(1):162

American Society of Hematology
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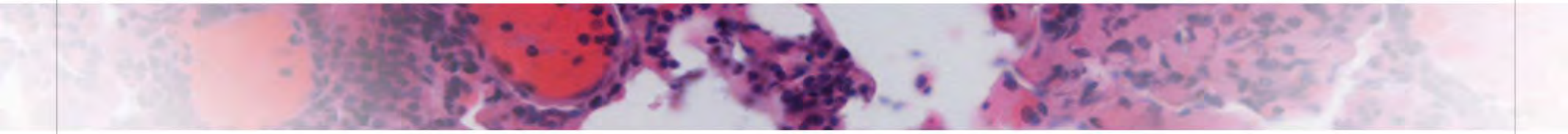
Oral abstract 238

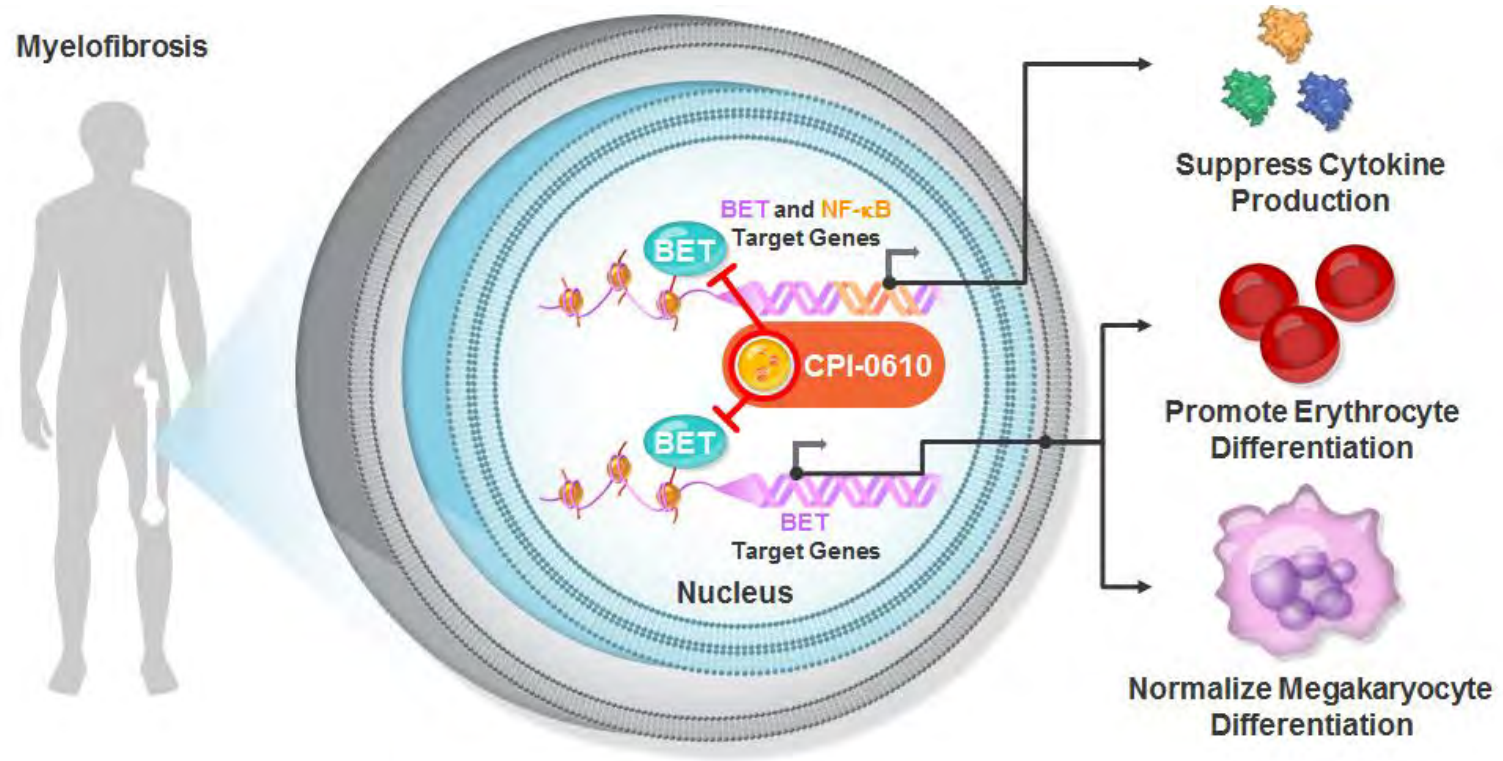


Pelabresib (CPI-0610) Combined With Ruxolitinib for JAK Inhibitor Treatment-Naïve Patients With Myelofibrosis: Durability of Response and Safety Beyond Week 24

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

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

Pelabresib in MF patients



Epigenetic modifier:

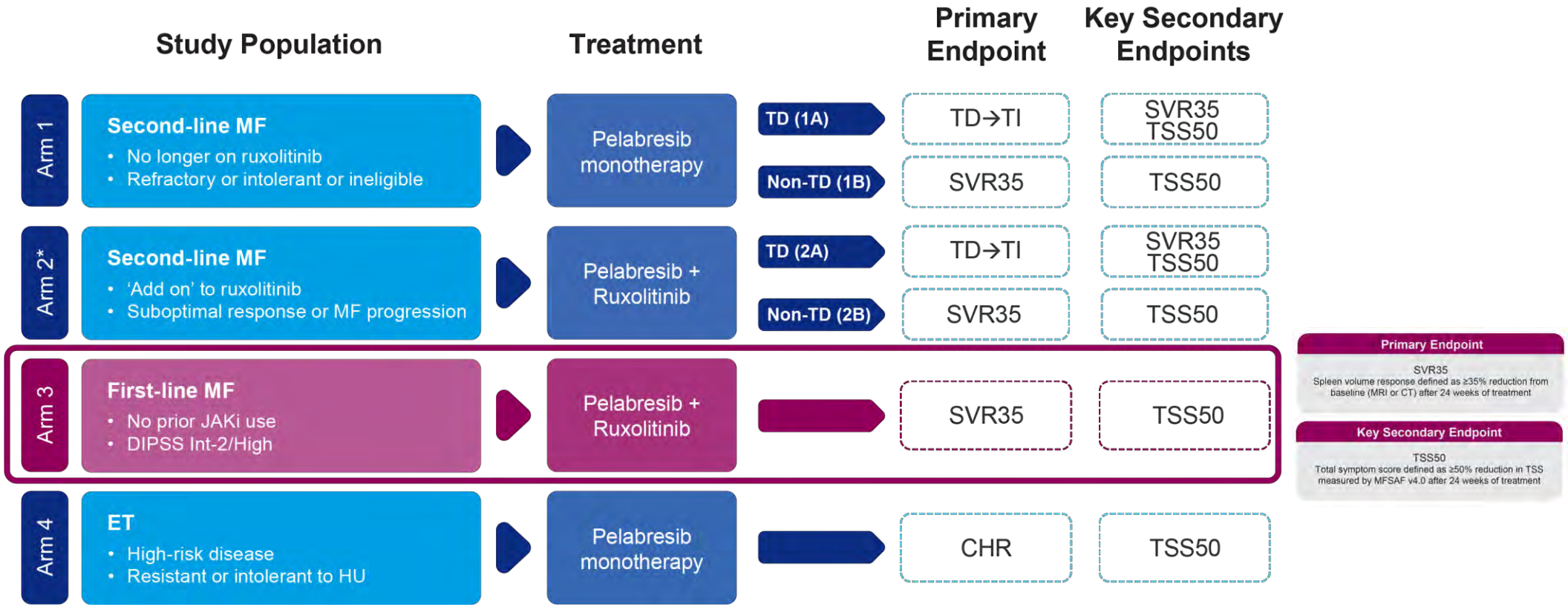
1. Preferentially targets transcription of key genes in cancer cells
2. Reduces inflammation and suppress cells in the bone marrow that drive myelofibrosis (MF)

Mascarenhas J et al. Annual American Society of Hematology Meeting, December 2020. Abstract 55.
Mascarenhas J et al. Pelabresib (CPI-0610) Combined With Ruxolitinib for JAK Inhibitor Treatment-Naïve Patients With Myelofibrosis: Durability of Response and Safety Beyond Week 24. Annual American Society of Hematology Meeting, December 2022. Oral abstract 238.

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

Promising results in combination with ruxolitinib

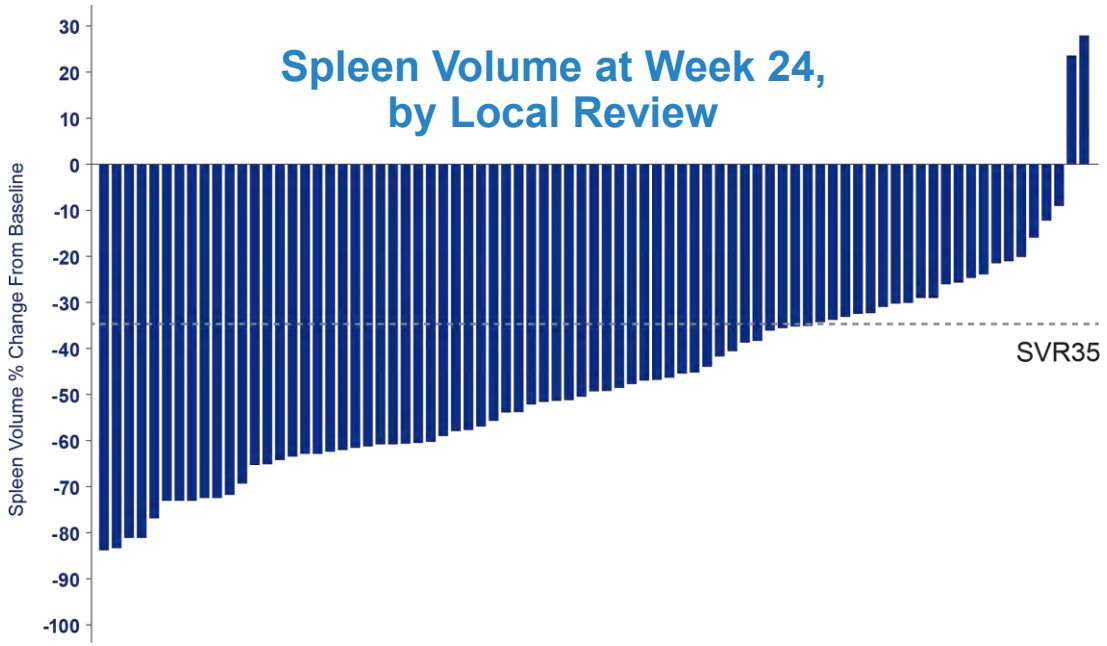
ARM 3: Updates on front-line pelabresib and ruxolitinib: N = 84

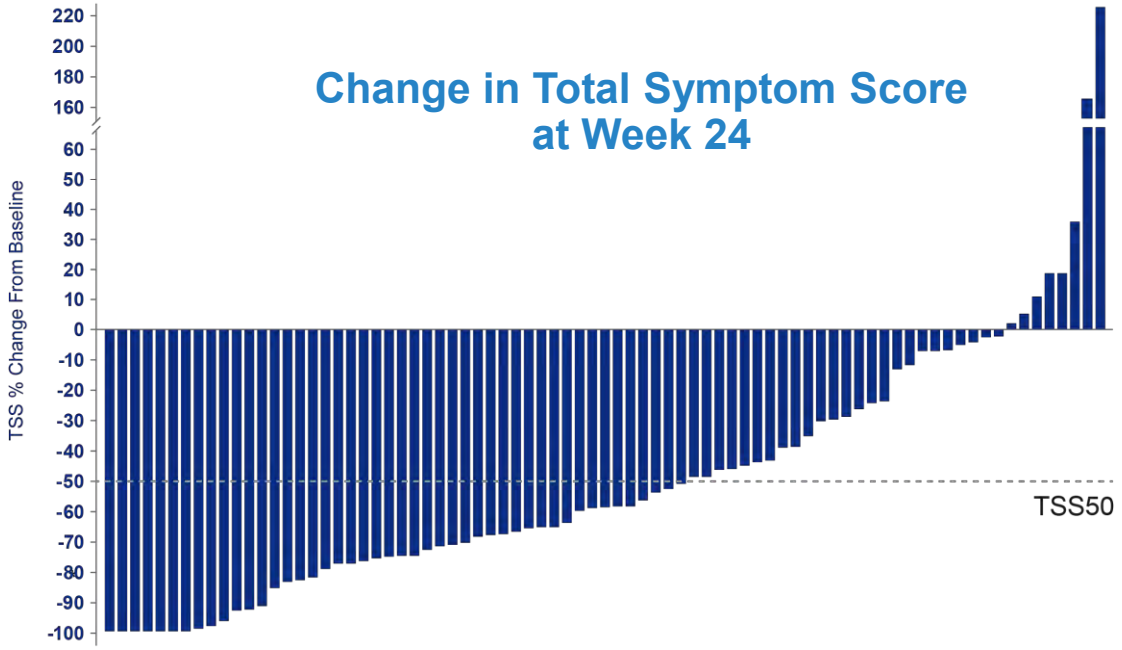


CHR, complete hematologic response; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; HU, hydroxyurea; Int-2, intermediate-2; JAKi, Janus kinase inhibitor; SVR35, ≥35% reduction in spleen volume at Week 24; TD, transfusion dependent; TI, transfusion independent; TSS50, ≥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. Annual American Society of Hematology Meeting, December 2022. Oral abstract 238.

MANIFEST Arm 3: spleen volume and total symptom score at week 24





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

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

Mascarenhas J et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 238.

MANIFEST Arm 3: Summary of adverse events

TEAEs of all grades that occurred in ≥20% of patients		All Grade N=84* n (%)	Grade 3 N=84* n (%)	Grade 4 N=84* n (%)
Hematologic Events	Anemia	36 (43%)	28 (33%)	1 (1%)
	Thrombocytopenia†	46 (55%)	12 (14%)	3 (4%)
Nonhematologic Events	**Gastrointestinal events**			
	Diarrhea	36 (43%)	2 (2%)	0
	Constipation	25 (30%)	0	0
	Nausea	24 (29%)	0	0
	Abdominal pain‡	22 (26%)	0	0
	Other nonhematologic events			
	Respiratory tract infection§	34 (41%)	8 (10%)	2 (2%)
	Asthenic conditions¶	32 (38%)	1 (1%)	1 (1%)
	Musculoskeletal pain**	27 (32%)	0	0
	Dizziness††	23 (27%)	0	0
	Cough	20 (24%)	0	0
	Dysgeusia	20 (24%)	0	0
	Dyspnea	19 (23%)	4 (5%)	0
	Headache	18 (21%)	0	0
	Muscle spasms	17 (20%)	0	0

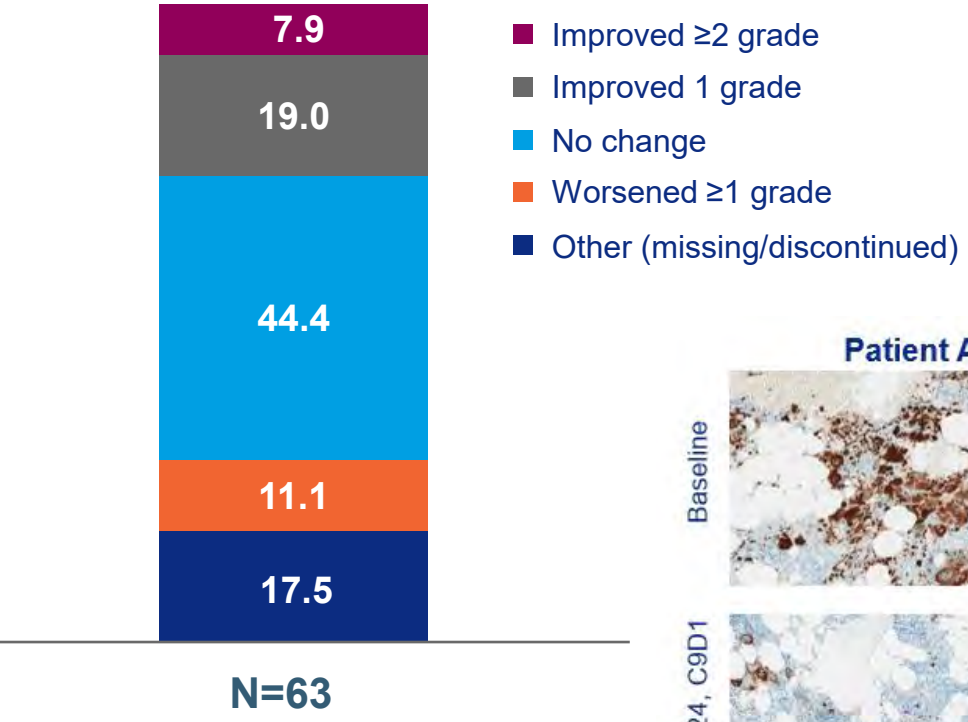
- Serious adverse events reported in ≥2 pts were anemia, pyrexia and COVID-19 (3 pts each), gastrointestinal hemorrhage, multiple organ dysfunction syndrome, COVID-19 pneumonia, pneumonia, respiratory tract infection, urinary tract infection, fall and respiratory failure (two pts each)
- Twelve pts (14%) reported TEAEs that led to pelabresib discontinuation
- Eight Gr 5 TEAEs were reported in 7 pts
  - Acute respiratory distress syndrome due to ruxolitinib withdrawal (2 pts each), multiorgan failure (MOF) due to COVID (reported as two separate TEAEs in the same pt), MOF due to sepsis secondary to pneumonia, respiratory failure due to COVID-19, bacterial endocarditis and urinary tract infection
  - All were assessed by PI as not related to pelabresib, except MOF due to sepsis secondary to pneumonia

*Safety-evaluable population: received at least one dose of study drug at the time of the data cut; †Includes TEAE platelet count decrease; ‡Includes TEAE abdominal pain upper; §Includes TEAEs of upper respiratory tract infection, viral upper respiratory tract infection, bronchitis, sinusitis, rhinitis, nasopharyngitis, pneumonia, COVID-19, COVID-19 pneumonia and influenza; ¶Include TEAEs of asthenia, fatigue, lethargy and malaise; **Includes TEAEs of arthralgia and myalgia; ††Includes TEAEs of balance disorder and vertigo.

Mascarenhas J et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 238.

MANIFEST Arm 3: Change in bone marrow fibrosis grade at Week 24 and *JAK2V617F* VAF

Change in Bone Marrow Fibrosis Grade at Week 24 by Central Pathology Review



- 27% (17/63) of patients showed ≥1 grade improvement at Week 24
  - This improvement was maintained in 59% (10/17) of patients at the next available assessment or longer
- 40% (25/63) of patients had ≥1 grade improvement at any time

- 18/47 (38%) patients reached ≥20% reduction in *JAK2 V617F* VAF
  - Median (min, max) reduction was –14% (–62%, 50%)

- 'Declustering' of megakaryocytes in the bone marrow and reductions in *JAK2 V617F* VAF correlated with SVR35 responses

Slide pairs were stained centrally for CD61; scanned and digital images were evaluated for CD61 distance. CD61 distance: mean distance between nuclei in a field with variable number of nuclei and up to 10 fields per image; QC review of each slide: each 400 mm^2 field must pass QC criteria.

Mascarenhas J et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 238.
Scandura J et al. Annual American Society of Hematology Meeting, December 2022. Poster abstract 630.

Novel therapeutic updates at ASH 2022

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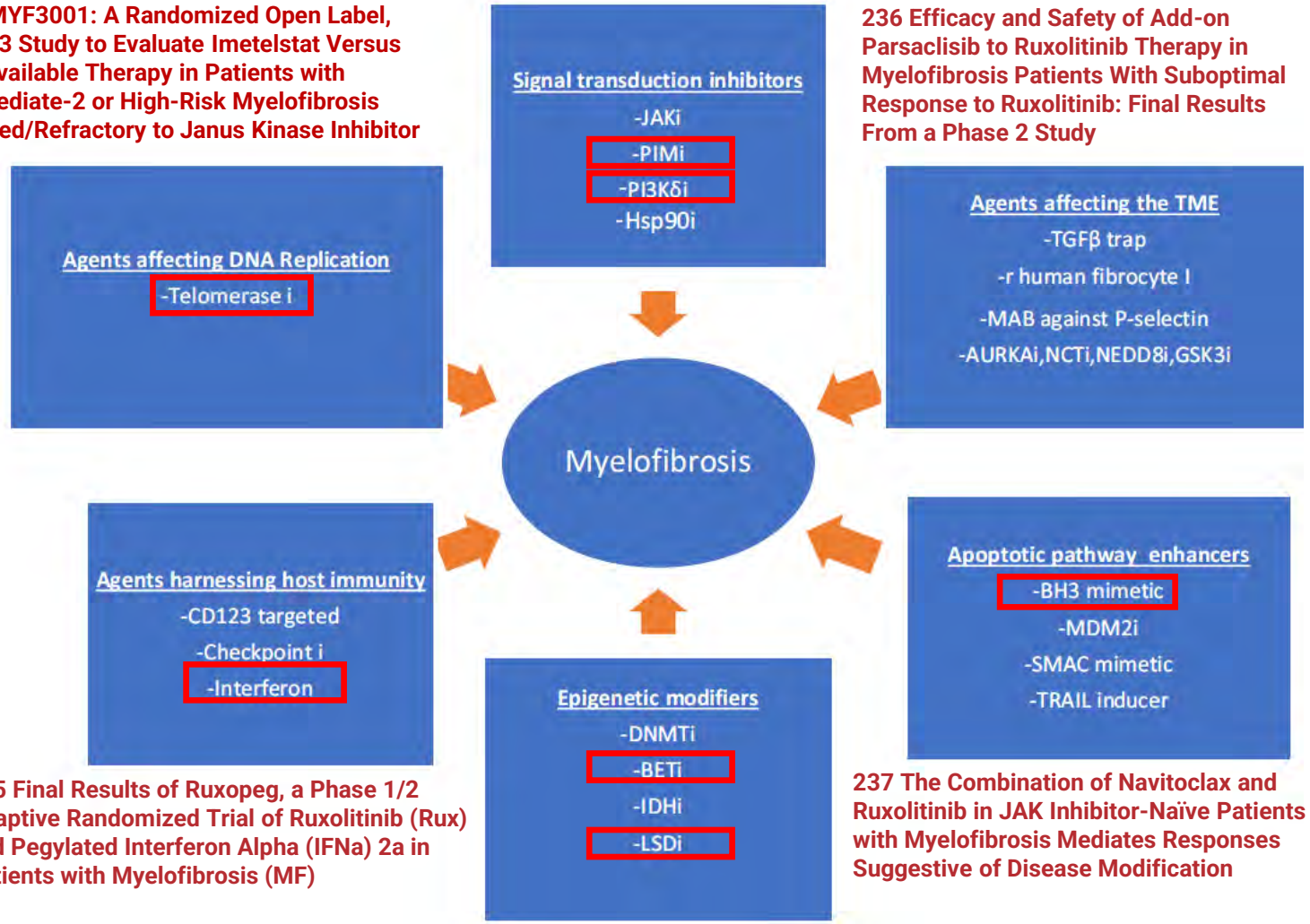

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4368 A Phase 2 Study of the LSD1 Inhibitor Bomedemstat (IMG-7289) for the Treatment of Advanced Myelofibrosis (MF): Updated Results and Genomic Analyses

- **Therapeutics combined with ruxolitinib frontline**
  1. INDEPENDENCE, phase 3, adding luspatercept to ruxolitinib-treated patients requiring RBC transfusions (NCT04717414)
  2. MANIFEST-2, phase 3, BET inhibitor pelabresib and ruxolitinib vs placebo and ruxolitinib (NCT04603495)
  3. TRANSFORM-1, phase 3, BCL-XL/BCL-2 inhibitor navitoclax and ruxolitinib vs placebo and ruxolitinib
- **"Add-on" agents to ruxolitinib in the 2nd line setting**
  1. TRANSFORM-2, phase 3, navitoclax and ruxolitinib in the 2nd line vs BAT in R/R MF
  2. LIMBER-304, phase 3, PI3 kinase inhibitor paraclisib and ruxolitinib vs placebo and ruxolitinib in patients with suboptimal response to ruxolitinib
- **Non-JAKi monotherapy 2nd line**
  - BOREAS, phase 3, navtemadlin, first-in-class HDM2 inhibitor (negative regulator of p53) vs BAT in patients refractory or resistant to JAKi
  - IMpactMF (MYF3001), phase 3, imetelstat in intermediate-2 or high-risk JAKi refractory

Adapted from Venugopal S and Mascarenhas. J Hematol Oncol. 2020 Dec 2;13(1):162

Learning objectives ASH 2022: Chronic Myeloid Leukemia

1. **Best strategies to treat chronic phase CML resistant or intolerant of 2nd generation TKIs**

2. **New therapeutics front-line**

Treatment Options in CP-CML

1. Best strategies to treat CP CML resistant or intolerant of 2nd generation TKIs

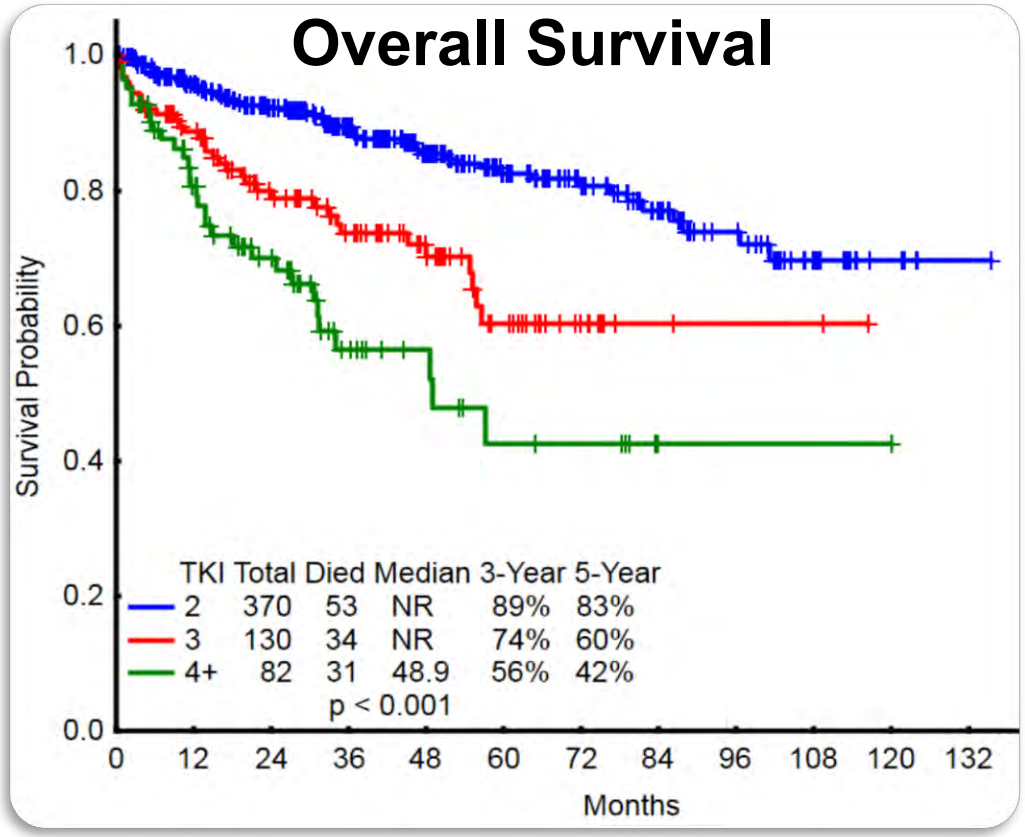
Compound	TKI Type / Generation	First Line	Second Line	≥ Third Line
Imatinib	ATP-competitive 1st generation	●		
Dasatinib	ATP-competitive 2nd generation	●	●	●
Nilotinib	ATP-competitive 2nd generation	●	●	●
Bosutinib	ATP-competitive 2nd generation	●	●	●
Ponatinib	ATP-competitive 3rd generation		●* **(T315I)**	●
Asciminib	ABL Myristoyl Pocket STAMP inhibitor		●† **(T315I)**	●
Omacetaxine	Protein synthesis inhibitor			●‡

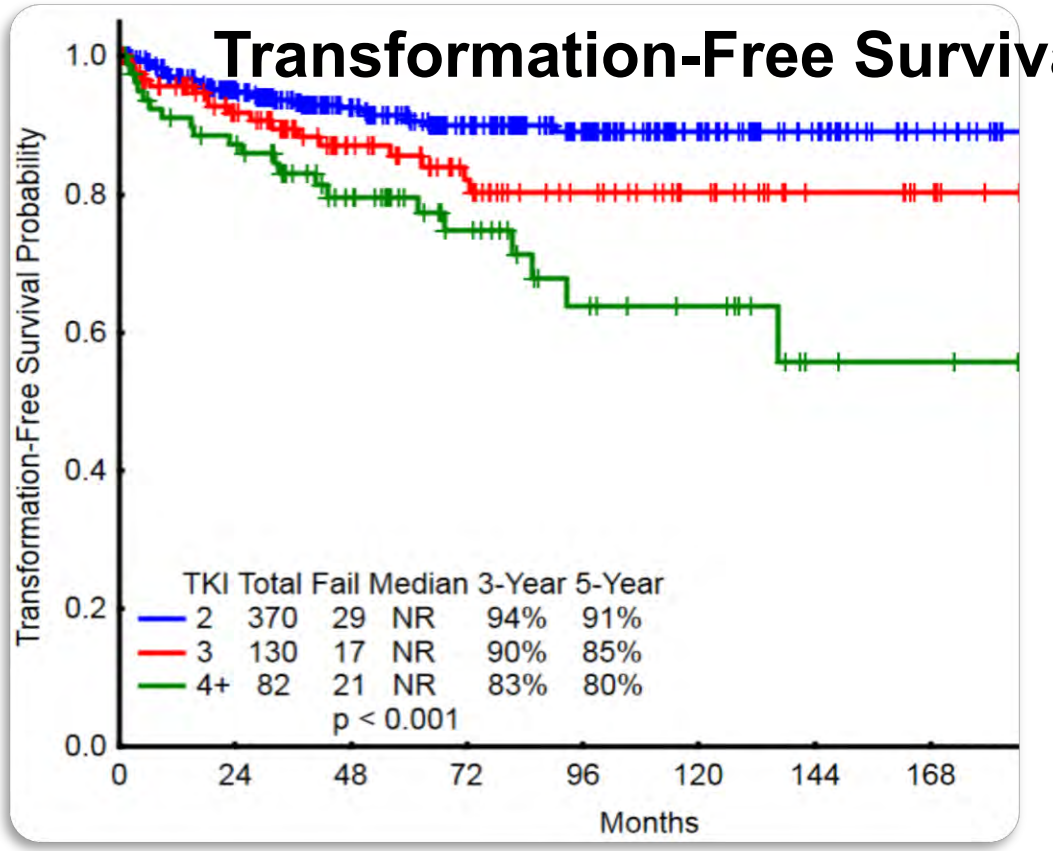
*Approved in US for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. †Approved only in US for a patients after ≥ 2 TKIs or for patients with T315I CP-CML in any line. ‡Only available in the US.

Hochhaus A, et al. *Leukemia* 2020; 34: 966-984; NCCN Guidelines. Chronic Myeloid Leukemia. V3.2022.

Outcomes for CP-CML patients on later lines of therapy

CML-related death increases with subsequent lines of therapy





- 582 CP CML patients at MD Anderson (2/2000 to 7/2015) who received > 1 TKI
- 2TKIs (n=370), 3TKIs (n=130), and 4+TKIs (n=82 ; 4 TKI n=59, 5 TKI n=20, 6 TKI n=1, 7 TKI n=2)

Akosile BA et al. ASH Annual Meeting Abstracts. Blood (2015) 126 (23): 1587.

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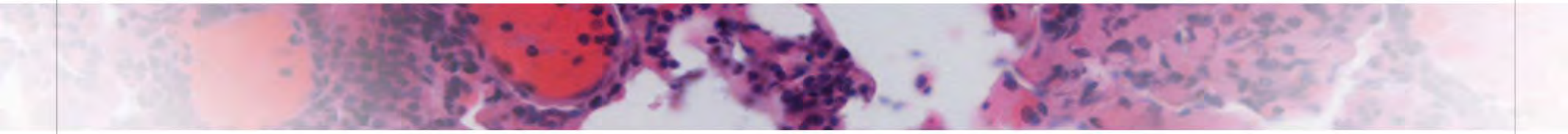
Oral abstract 620



Three-year update from the OPTIC trial: A dose-optimization study of 3 starting doses of ponatinib

Jorge Cortes,[1] Michael Deininger,[2] Elza Lomaia,[3] Beatriz Moiraghi,[4] Maria Undurraga Sutton,[5] Carolina Pavlovsky,[6] Charles Chuah,[7] Tomasz Sacha,[8] Jeffrey H. Lipton,[9] James McCloskey,[10] Andreas Hochhaus,[11] Philippe Rousselot,[12] Gianantonio Rosti,[13] Hugues de Lavallade,[14] Christine Rojas,[15] Anna Turkina,[16] Lori Maness,[17] Moshe Talpaz,[18] Michael Mauro,[19] Vickie Lu,[20] Alexander Vorog,[20] Jane Apperley[21]

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Phase 2 OPTIC trial of ponatinib

FDA Label Change

What is the optimal ponatinib dose to maintain efficacy but minimize AOEs?

- Median (range) duration of follow-up was 54 months (0–80)

Primary endpoint:
≤1% *BCR::ABL1*^{IS} ***at*** 12 months

Enrolled N=283

- Adult patients with CP-CML
- Resistant/intolerant to 2 or more prior TKIs or *BCR::ABL1* T315I mutation-positive
- >1% *BCR::ABL1*^{IS}

Randomization 1:1:1

Cohort A: 45 mg → 15 mg QD[a]

Cohort B: 30 mg → 15 mg QD[a]

Cohort C: 15 mg QD[a]

Dose reduction to 15 mg daily upon achievement of ≤1% *BCR::ABL1*^{IS}

Dose reduction to 10 mg daily if AEs

- **More than 50% of the patients had received 3 or more TKIs**
- **More than 90% were resistant to their last TKI**

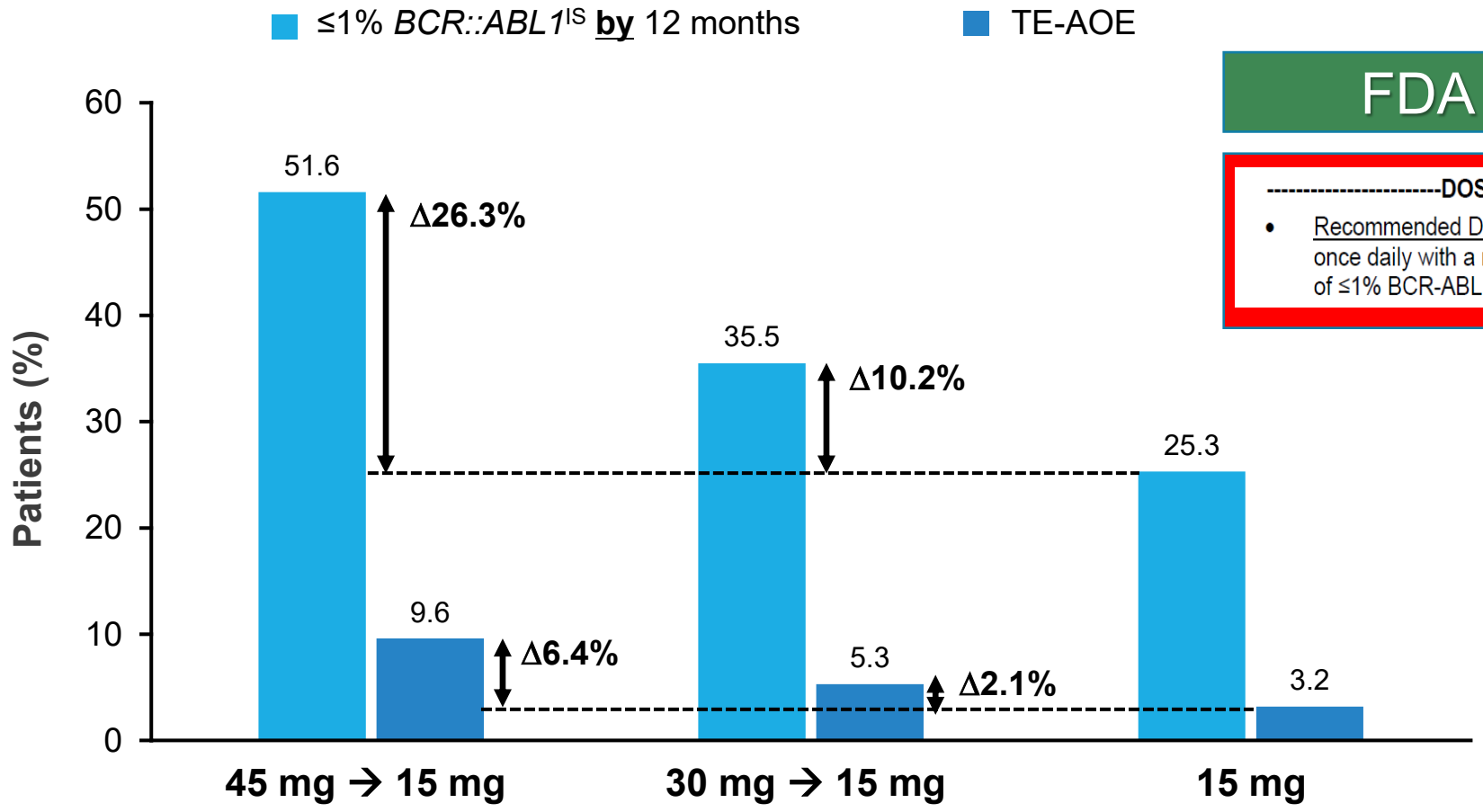
[a] Dose reductions due to AEs were permitted

→15 mg, Cohort A is referred to as 45 mg → 15 mg and Cohort B as 30 mg → 15 mg because the study design has a dose reduction to 15 mg upon achievement of ≤1% BCR-ABL1^{IS}. There also were patients in Cohorts A and B who dose-reduced to different dose levels (30, 15, and 10 mg) due to safety

IA, interim analysis; ITT, intent to treat; QD, daily; TEAE, treatment-emergent adverse event

Cortes J et al. Blood. 2021 Nov 25;138(21):2042-2050.

OPTIC: Overall Safety and Efficacy by Starting Dose



FDA Label Change

----------DOSAGE AND ADMINISTRATION----------

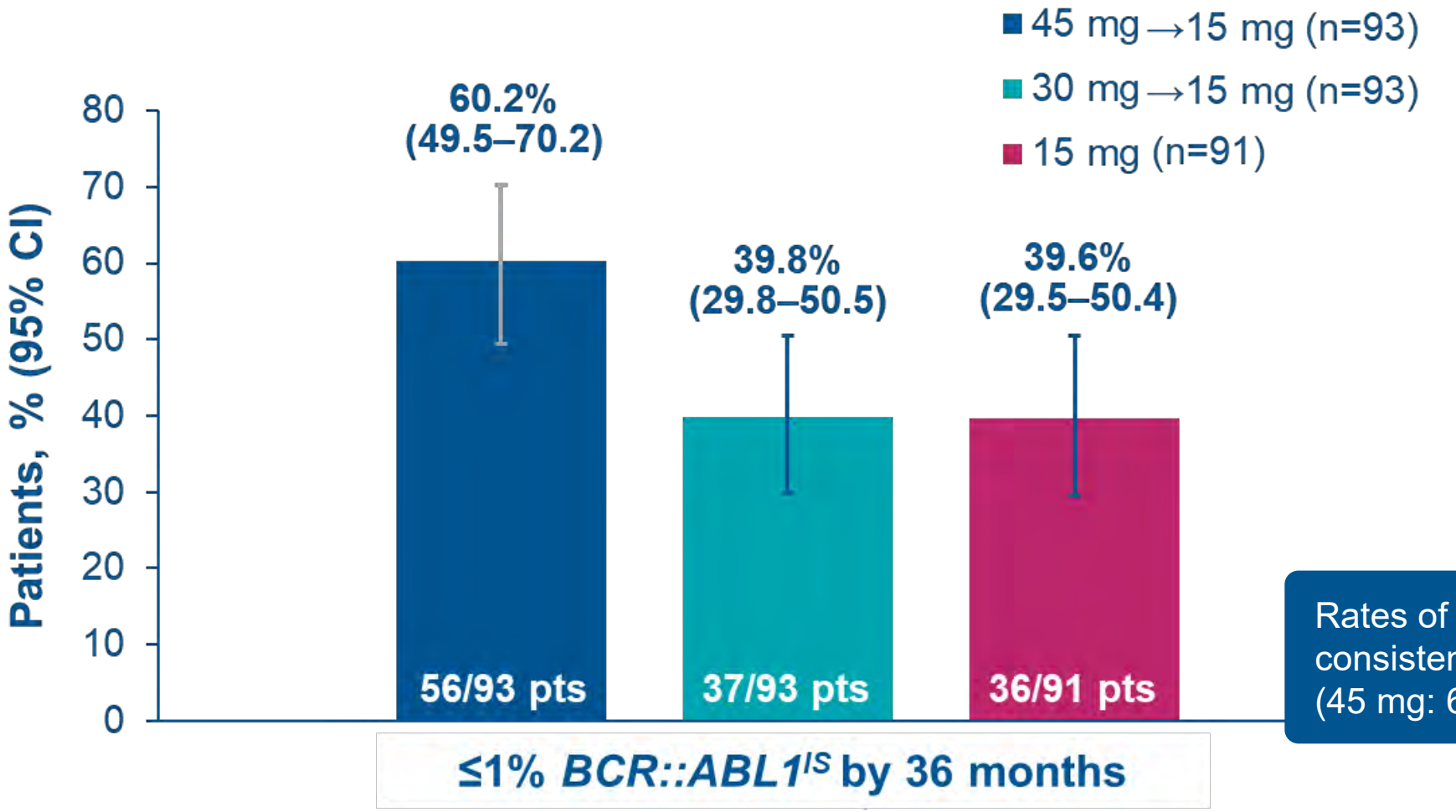
- Recommended Dosage in CP-CML: Starting dose is 45 mg orally once daily with a reduction to 15 mg once daily upon achievement of ≤1% BCR-ABL1^{IS}. (2.1)

Dose dependent impact on AOEs was observed BUT there was a lower the incidence of AOEs relative to what was observed in the PACE study (9.6% in the 45 mg arm) which did not include dose reduction

The primary end point (≤1% *BCR::ABL1*^{IS} **at** 12 months) was achieved in 44.1% (31.7-57.0) in the 45-mg cohort, 29.0% (18.4-41.6) in the 30-mg cohort, and 23.1% (13.4-35.3) in the 15-mg cohort.

Cortes J, et al. *Blood*. 2021;138(21):2042-2050.

≤1% *BCR::ABL1*^{IS} response rate by 36 months



- At the first interim analysis of OPTIC, the primary endpoint of ≤1% *BCR::ABL1*^{IS} at 12 months was highest with the 45 mg➔15 mg regimen (44.1% [98.3% CI: 31.7–57.0]), which met the prespecified statistical endpoint (equivalent to *P*-value <0.017)
- As of May 9, 2022, median duration of response was not reached for patients in any treatment arm

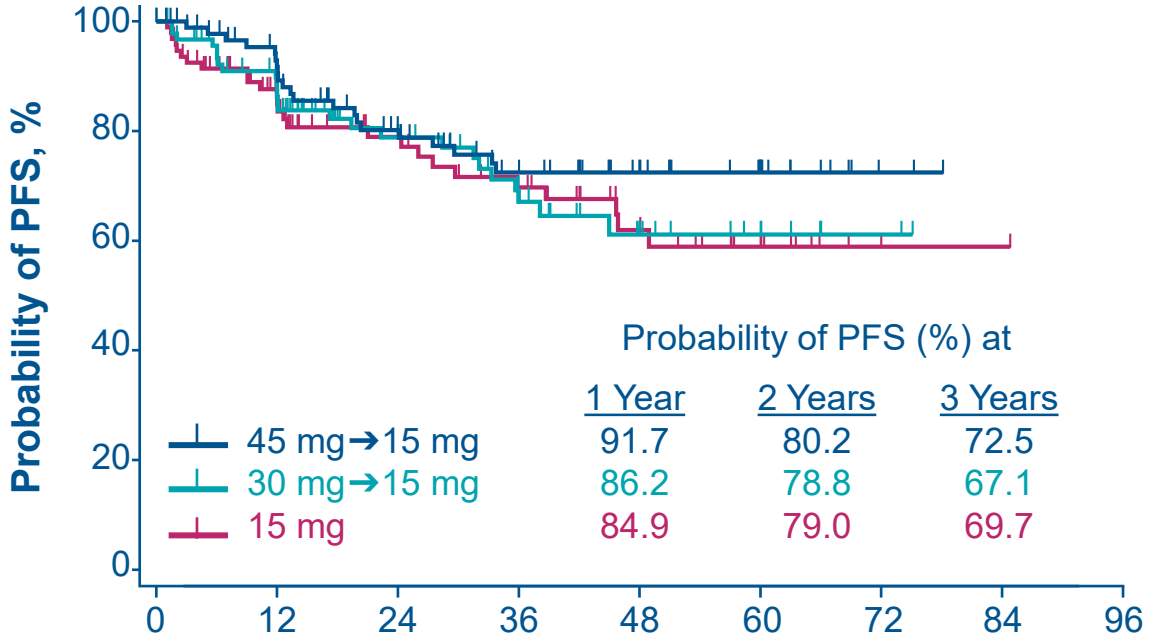
Rates of grade 3–5 TE-AOEs were consistent with the OPTIC primary analysis (45 mg: 6%; 30 mg: 6%; 1 mg: 4%)

CI, confidence interval; IS, International Standard ratio; pts, patients

Cortes J et al. Three-year update from the OPTIC trial: a dose-finding optimization study of 3 starting doses of ponatinib. Annual American Society of Hematology Meeting, December 2022. Oral abstract 620.

Kaplan-Meier–estimated probability of PFS and OS by ponatinib dosing regimen

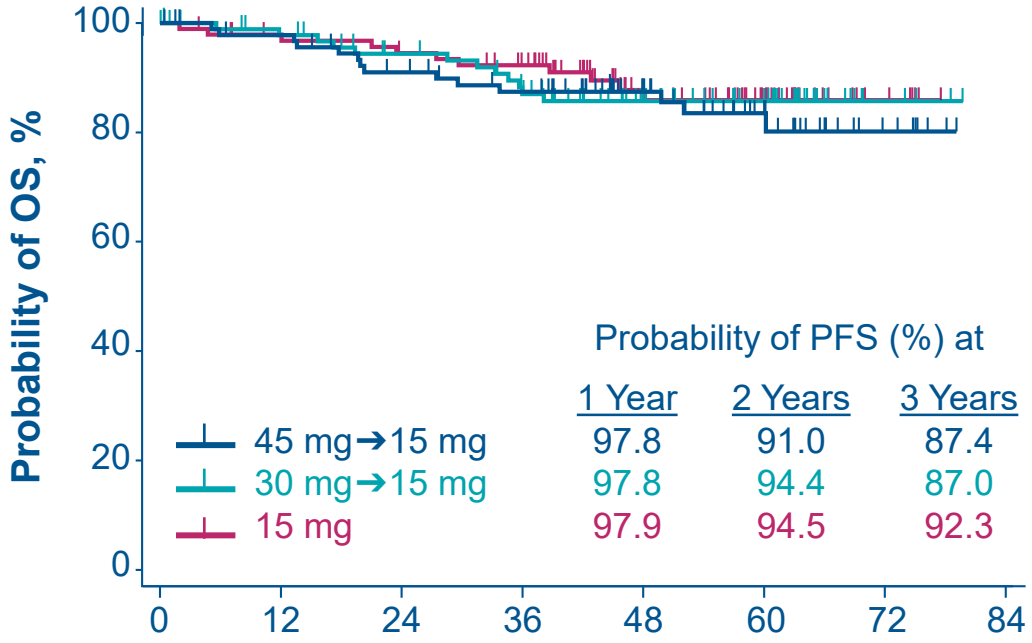
PFS



No. at risk

45 mg	94	75	57	43	27	17	2	0	0
30 mg	95	73	46	32	16	9	2	0	0
15 mg	94	64	45	36	22	12	1	1	0

OS



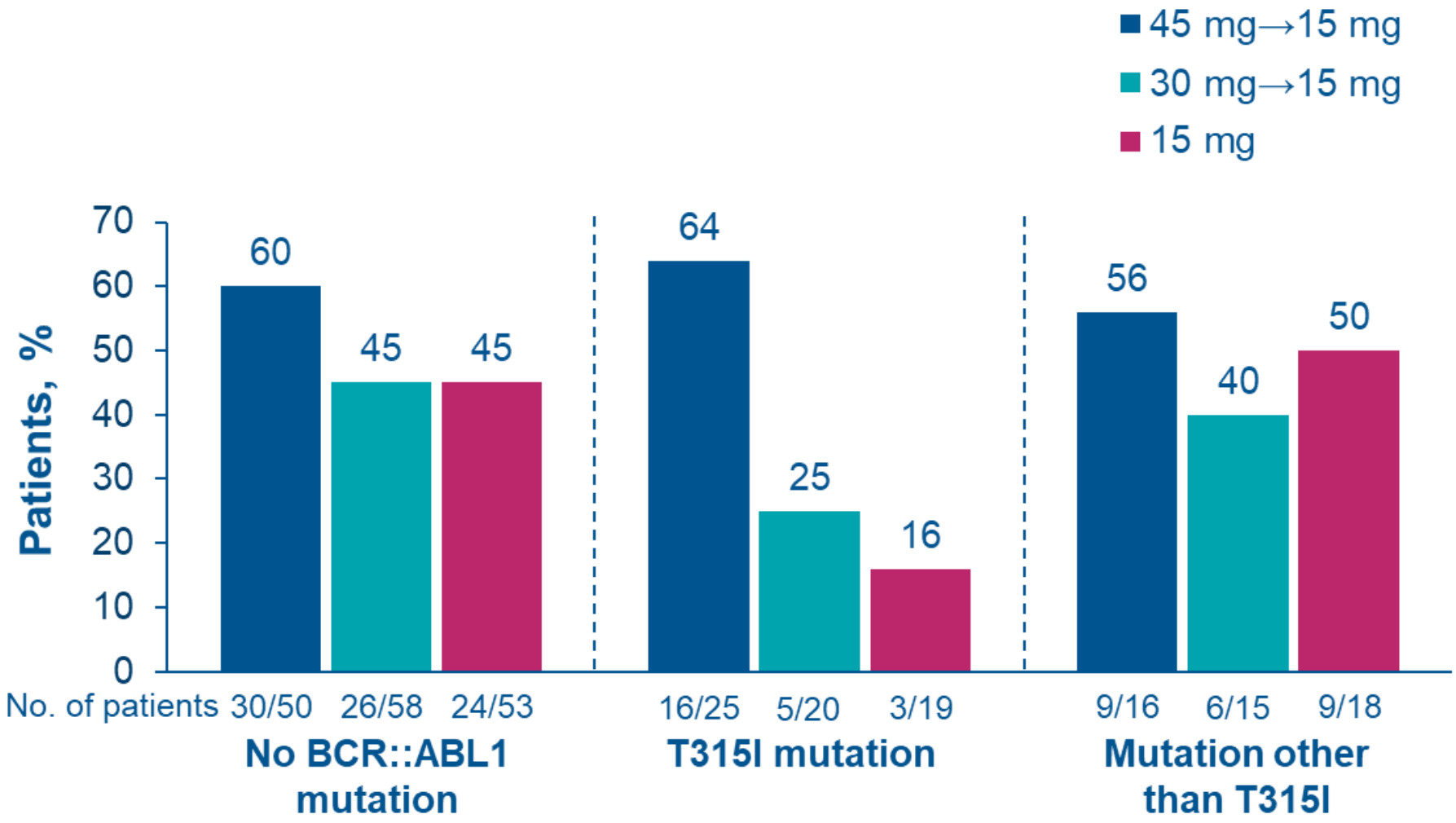
No. at risk

45 mg	94	88	79	72	50	30	7	0
30 mg	95	88	79	70	45	32	4	0
15 mg	94	88	84	78	47	27	6	0

OS, overall survival; PFS, progression-free survival

Cortes J et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 620.

≤1% *BCR::ABL1*^{IS} response rate by 36 months by BCR::ABL1 mutation status at baseline

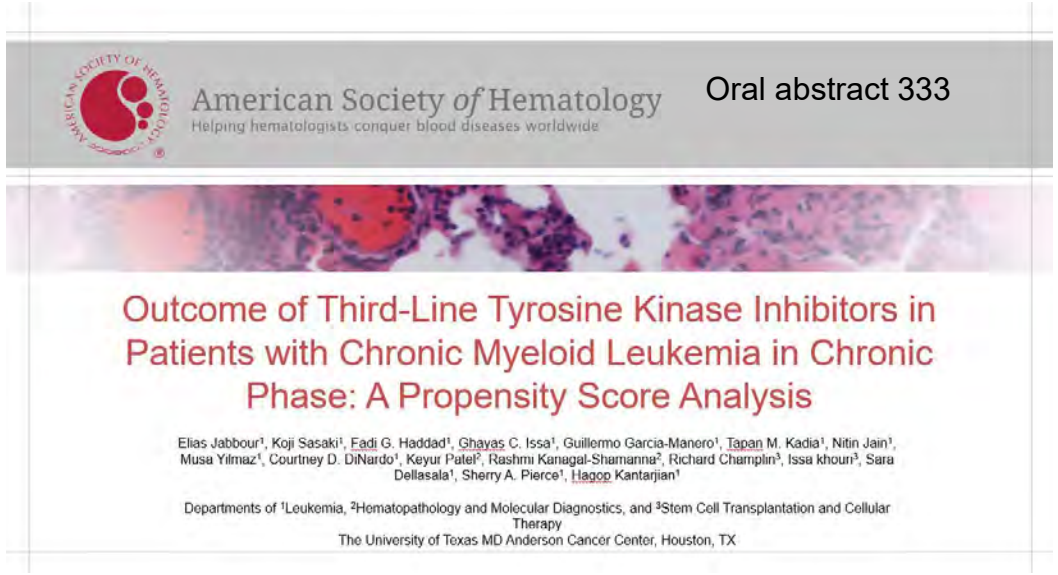


- Patients in the 30 mg➔15 mg and 15 mg cohorts without the T315I mutation had greater clinical benefit than patients with the T315I mutation
- Response rates in the 45 mg➔15 mg cohort were similar regardless of *BCR::ABL1* mutation status

IS, International Standard ratio

Cortes J et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 620.

Best 3rd line therapy: ponatinib or 2G TKI?

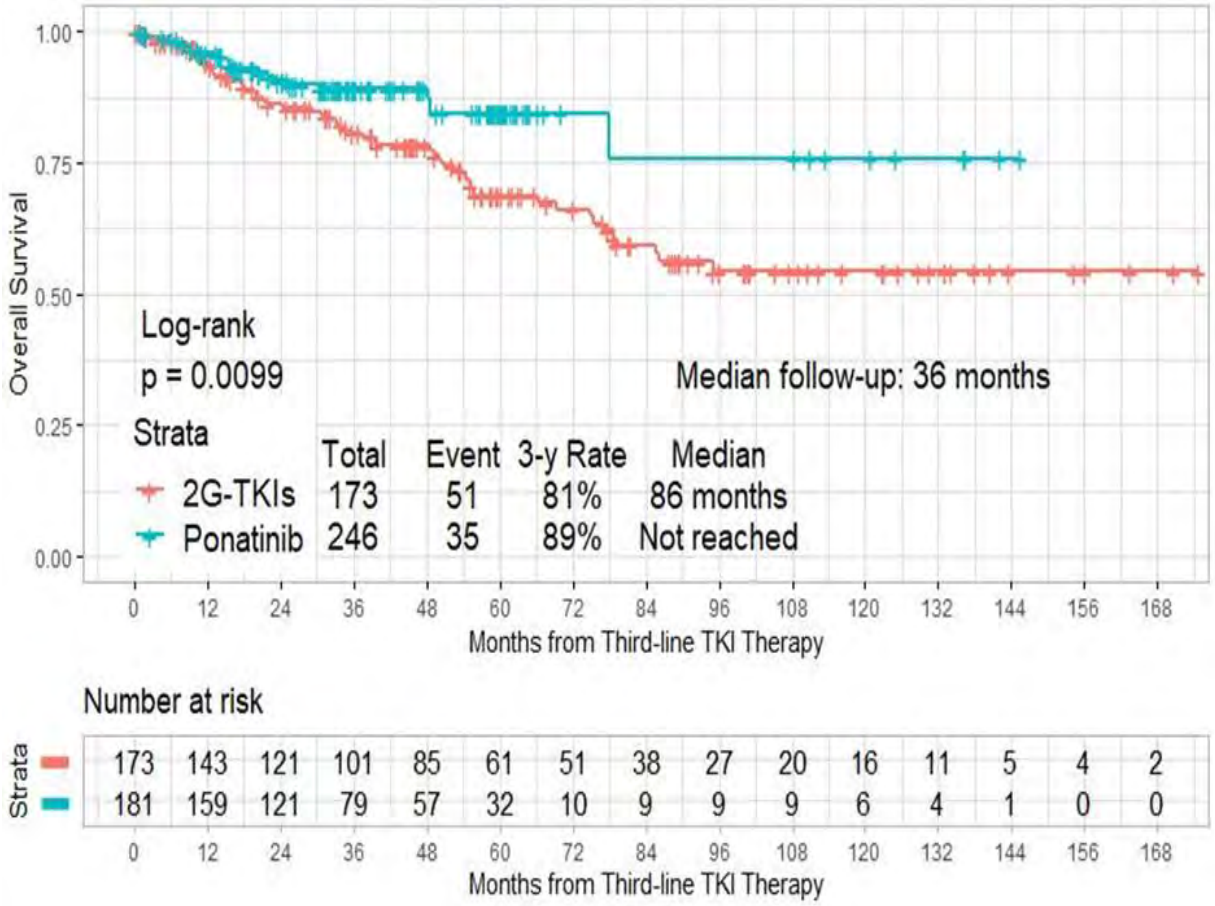


- Retrospective analysis of 354 patients with CML-CP treated with 3rd line TKIs:
  - At MD Anderson (n=204)
  - In the OPTIC (n=87) and PACE (n=63) trials
- Exclusion of patients with T315I mutation
- Differences in baseline response status ➔ Assessment of the relative logarithmic *BCR::ABL1* change from baseline to best response
- Relative logarithmic changes divided into less than 1 log reduction, 1 log reduction, 2 log reductions, 3+ log reductions
- One-to-one propensity score matching was performed using matching covariates:
  - age at the time of third-line therapy, gender, race/ethnicity, comorbidity, prior TKI therapy, duration of prior TKI therapy, best prior response during the frontline and second-line TKI therapy, body mass index, white blood cell count, platelet count, percentages of basophils and blasts in peripheral blood, and *BCR::ABL1* levels.

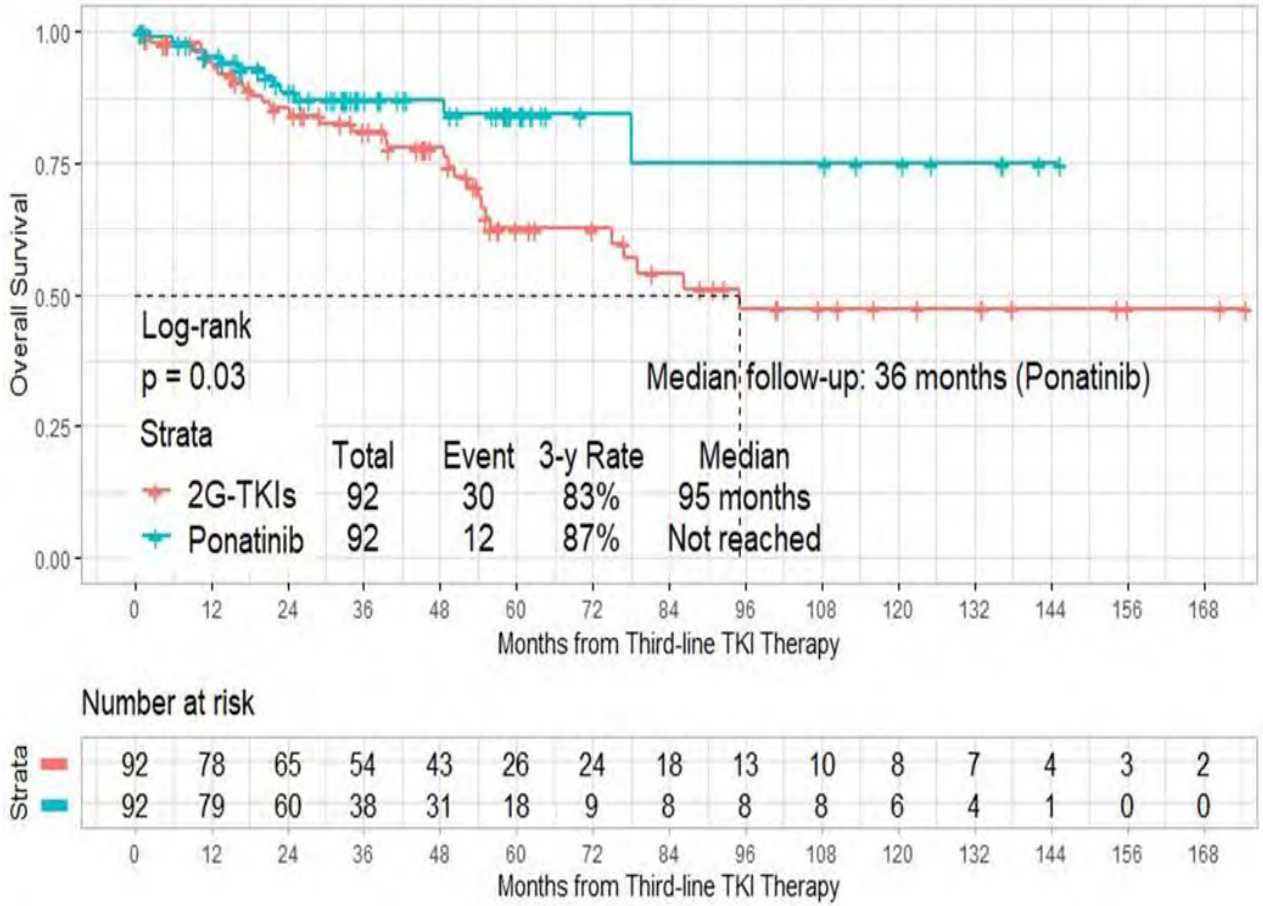
Jabbour E et al. Outcomes of third-line tyrosine kinase inhibitors in patients with chronic myeloid leukemia in chronic phase: a propensity score analysis. Annual American Society of Hematology Meeting, December 2022. Oral abstract 333.

Third-line TKI in CML: OS by Third-line TKI Before and After Propensity Score Matching

Before matching



After matching



Median follow-up 46 months

Jabbour E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 333.

Conclusions

- Ponatinib is superior to 2G-TKIs in the 3rd line setting in retrospective analysis:
  - Cumulative 2-log reduction in *BCR::ABL1* - 51% vs 34%
  - Before propensity matching: 3-year PFS 81% vs 60%; 3-year OS 89% vs 81%
  - After propensity matching: 3-year PFS 83% vs 59%; 3-year OS 87% vs 83%

- In patients with *BCR::ABL1* >1%:
  - Before propensity matching: 3-year PFS 81% vs 51%; 3-year OS 89% vs 80%
  - After propensity matching: 3-year PFS 83% vs 44%; 3-year OS 88% vs 80%

Jabbour E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 333.

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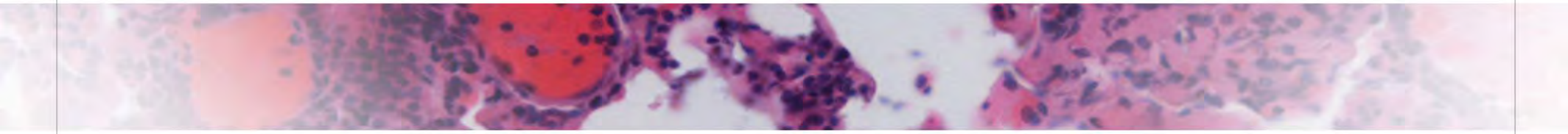

Olverembatinib (HQP1351) overcomes ponatinib resistance in patients with heavily pretreated/refractory chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL)

E Jabbour,[1] PB Koller,[2] VG Oehler,[3] OH Jamy,[4] S Mukherjee,[5] AM Hunter,[6] MR Baer,[7] JT Beck,[8] Z Chen,[9] HS Guo,[10] L Fu,[11] LC Men,[9] L Jiang,[11] CL Wang,[11] HB Wang,[9] DJ Yang,[9-12] YF Zhai,[9-11*] and H Kantarjian[1*]

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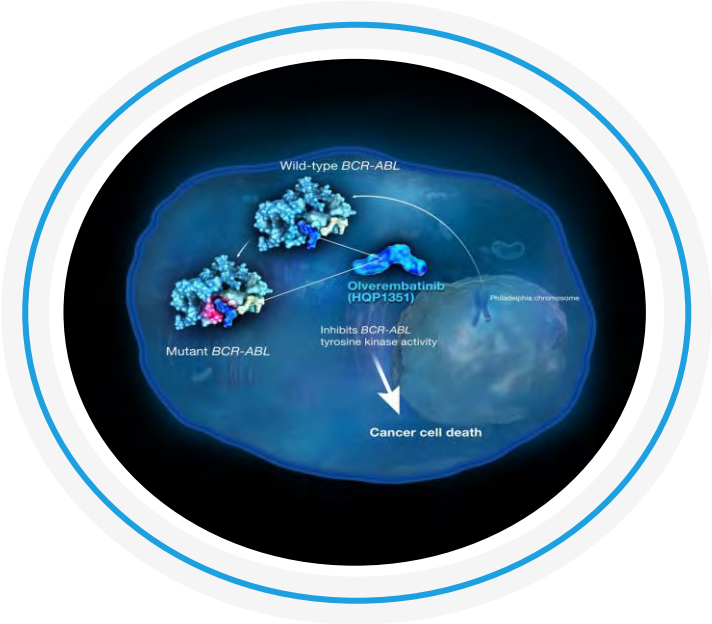
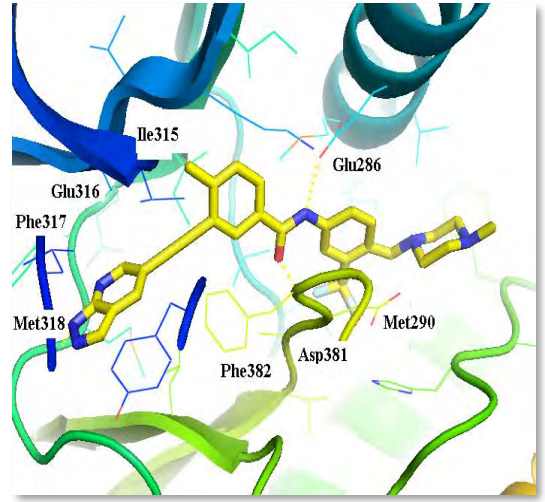
[*]Correspondence: yzhai@ascentage.com; hkantarjian@mdanderson.org

Olverembatinib in Resistant CML: Background

- Novel 3G TKI with activity in CML and Ph+ ALL
- Highly potent vs *BCR::ABL1*^{WT} and *BCR::ABL1*^{T315I} mutant kinases, including compound mutations
- Strong effects on multiple kinases: KIT, PDGFR, SRC, FGFR, and FLT3
- Updates of 101 CP and AP CML patients in China reported CCyR in 69% and MMR in 54% of CP patients





Approved by the China National Medical Products Administration (NMPA)

Ren X, et al. J Med Chem. 2013,14;56:879-894
Jabbour E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 82.

Olverembatinib in Resistant CML: Study Design

- **Primary endpoint: pharmacokinetics (PK)**
- **Key secondary endpoints: safety and efficacy**

Key study criteria

- Adults with CML-CP, AP, BP, or Ph$^+$ ALL
- Resistance or intolerance to ≥2 *BCR::ABL1* inhibitors*
- ECOG PS ≤ 2
- Adequate cardiac/ hepatic/renal function
- Exclude patients with CML-CP who have CCyR

HQP1351CU101 (NCT04260022)

Randomized 3:3:2

(stratified by leukemia phases and *T315I* mutation status at baseline)

N = 51**

- Olverembatinib 30 mg QOD, n = 21
- Olverembatinib 40 mg QOD, n = 19
- Olverembatinib 50 mg QOD, n = 10

Treatment and follow-up

28 days per cycle

CML-AP, CML in accelerated-phase; **CMP-BP**, CML in blast-phase; **CML-CP**, CML in chronic phase;
CCyR, complete cytogenetic response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **QOD**, every other day.
*For patients with a T315I mutation, the number of pretreated *BCR::ABL1* inhibitors was not restricted.
** Two patient has been screened successfully but not dosed yet.

Jabbour E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 82.

Olverembatinib in Resistant CML:

Patients (N = 51)

Characteristic	CML-CP	Advanced Ph+ leukemia	Total
N	**38**	**13**	**51**
Median (range) age, yr	44 (21-75)	62 (34-79)	51 (21-79)
Sex, male, n (%)	21 (55.3)	7 (53.8)	28 (54.9)
Race, n (%)			
White	33 (86.8)	8 (61.5)	41 (80.4)
Black or African American	4 (10.5)	2 (15.4)	6 (11.8)
Asian	0	3 (23.1)	3 (5.9)
Unavailable/unknown	1 (2.6)	0	1 (2.0)
ECOG PS, n (%)			
0	16 (42.1)	5 (38.5)	21 (41.2)
1	11 (28.9)	3 (23.1)	14 (27.5)
2	1 (2.6)	1 (7.7)	2 (3.9)
Not done	10 (26.3)	4 (30.8)	14 (27.5)
# of Patients with CV Comorbidity, n (%)	19 (50.0)	9 (69.2)	28 (54.9)
Hypertension	12 (31.6)	6 (46.2)	18 (35.3)

Jabbour E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 82.

Olverembatinib in Resistant CML:

Patients (N = 51)

Characteristic	CML-CP	Advanced Ph+ leukemia	Total
N	**38**	**13**	**51**
Line of therapy, n. (%)			
Primary refractory	0	0	0
Salvage 1	6 (15.8)	1 (7.7)	7 (13.7)
Salvage 2	11 (28.9)	3 (23.1)	14 (27.5)
Salvage 3+	18 (47.4)	7 (53.8)	25 (49.0)
Missing	3 (7.9)	2 (15.4)	5 (9.8)
Prior ponatinib use, n (%)	20 (52.6)	8 (80.0)	28 (54.9)
Resistant	14 (70.0)	7 (87.5)	21 (75.0)
Intolerant	6 (30.0)	1 (12.5)	7 (25.0)
T315I mutation	14 (36.8)	5 (38.5)	19 (37.3)

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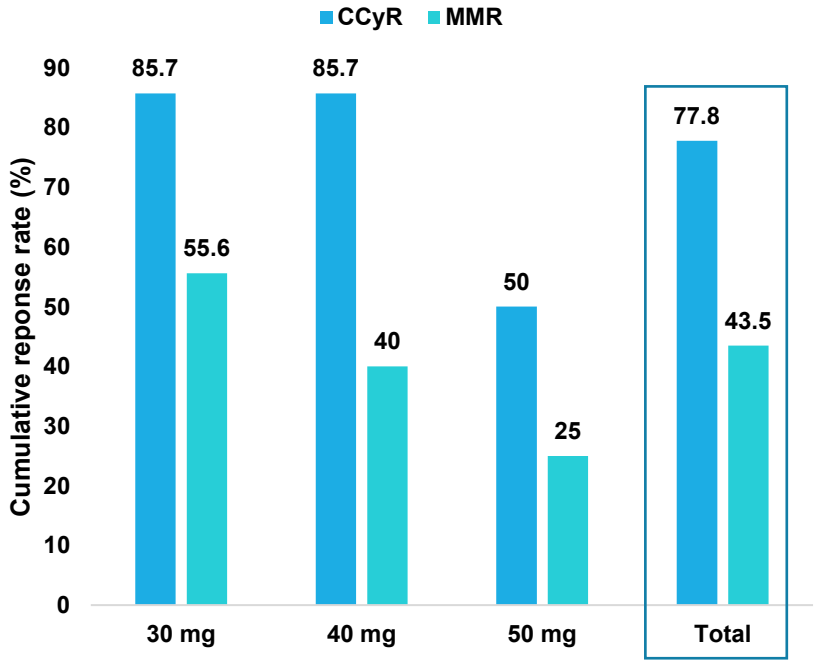
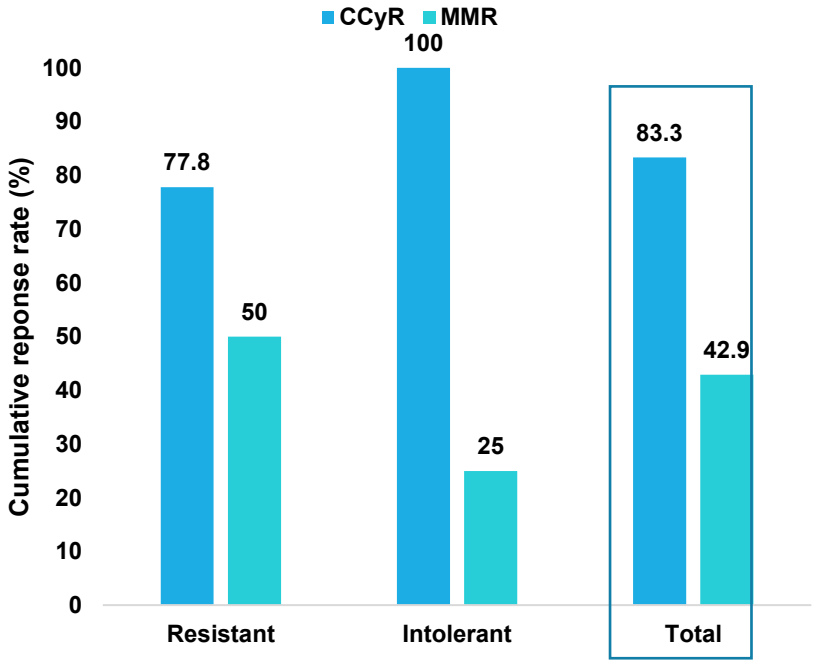
Olverembatinib in Resistant CML-CP:
Response Rates (n=23)

CML-CP by dose



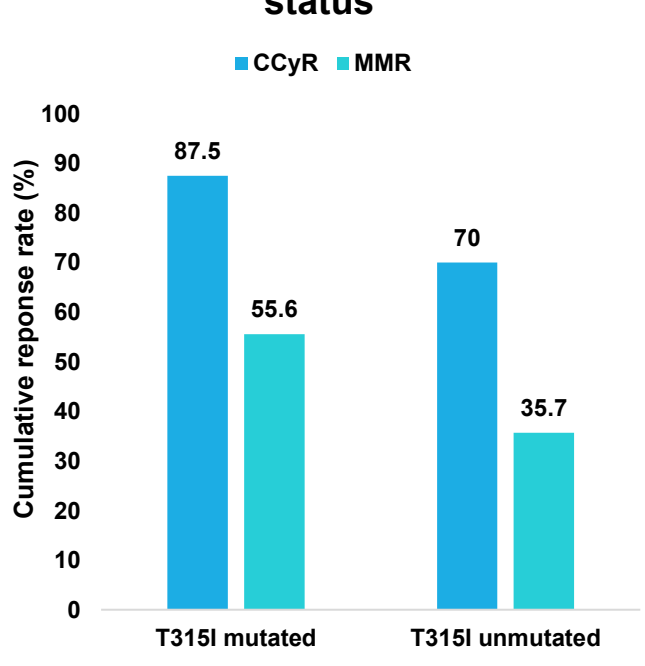
	30 mg	40 mg	50 mg	Total
CCyR	85.7 (6/7)	85.7 (6/7)	50 (2/4)	77.8 (14/18)
MMR	55.6 (5/9)	40 (4/10)	25 (1/4)	43.5 (10/23)

CML-CP ponatinib-failed



	Resistant	Intolerant	Total
CCyR	77.8 (7/9)	100 (3/3)	83.3 (10/12)
MMR	50 (5/10)	25 (1/4)	42.9 (6/14)

CML-CP by T315I mutation status

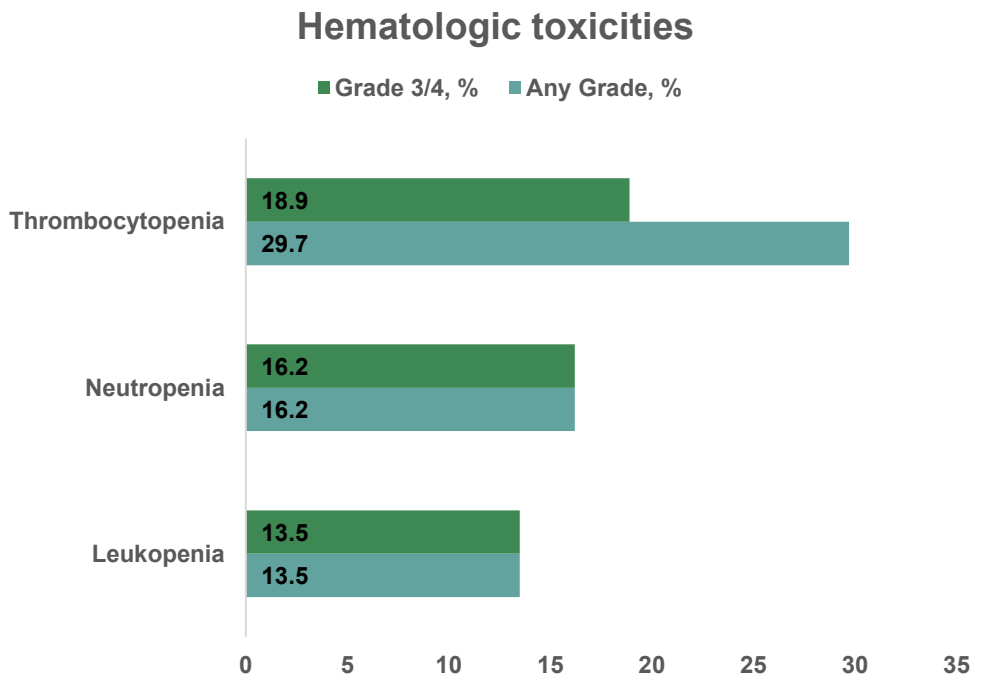


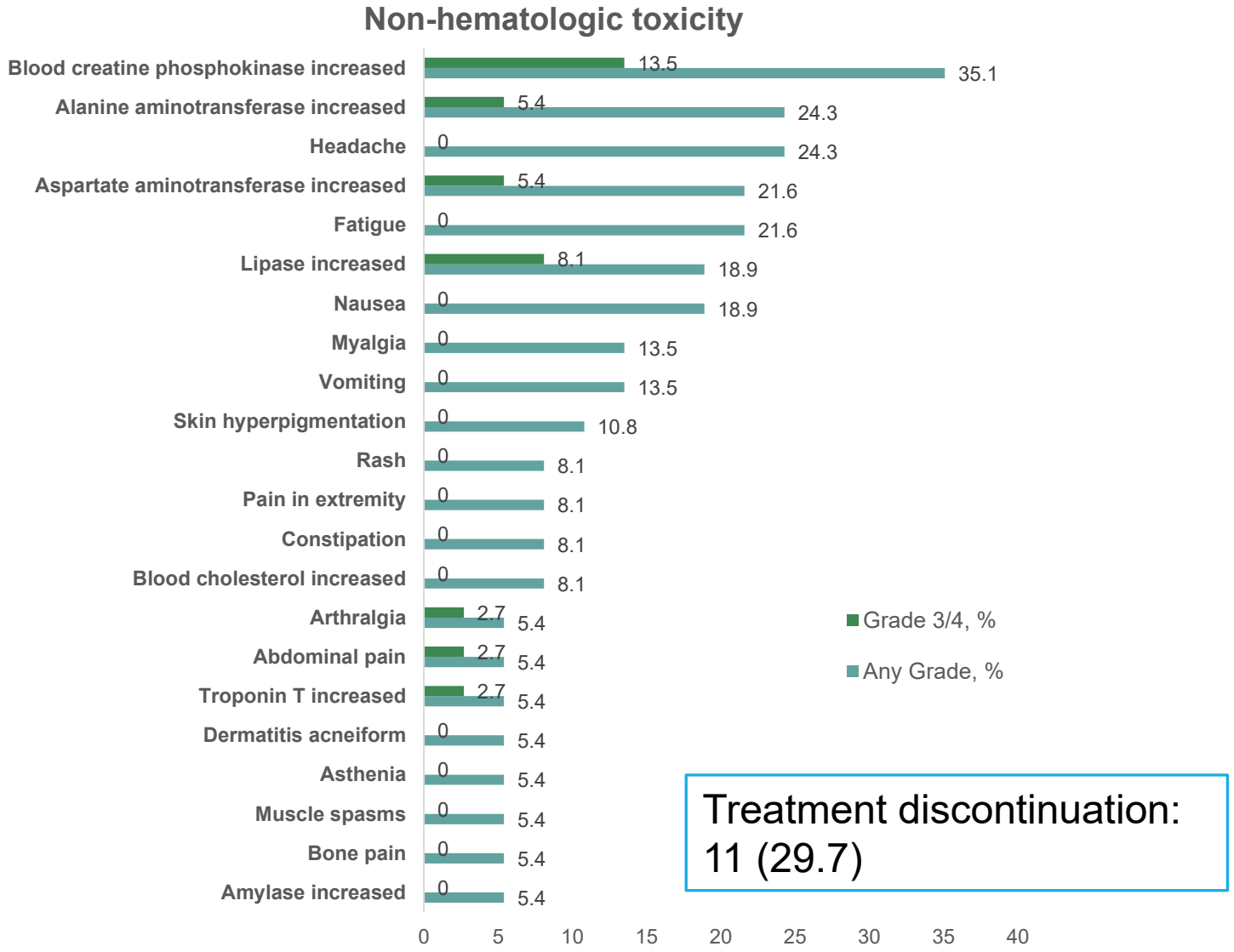
	T315I mutated	T315I unmutated
CCyR	87.5 (7/8)	70 (7/10)
MMR	55.6 (5/9)	35.7 (5/14)

Jabbour E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 82.

Olverembatinib in Resistant CML: Safety

Related Adverse Events (≥ 5% any grade; n = 37)





Rate of AOEs appears low with limited follow-up

Treatment discontinuation: 11 (29.7)

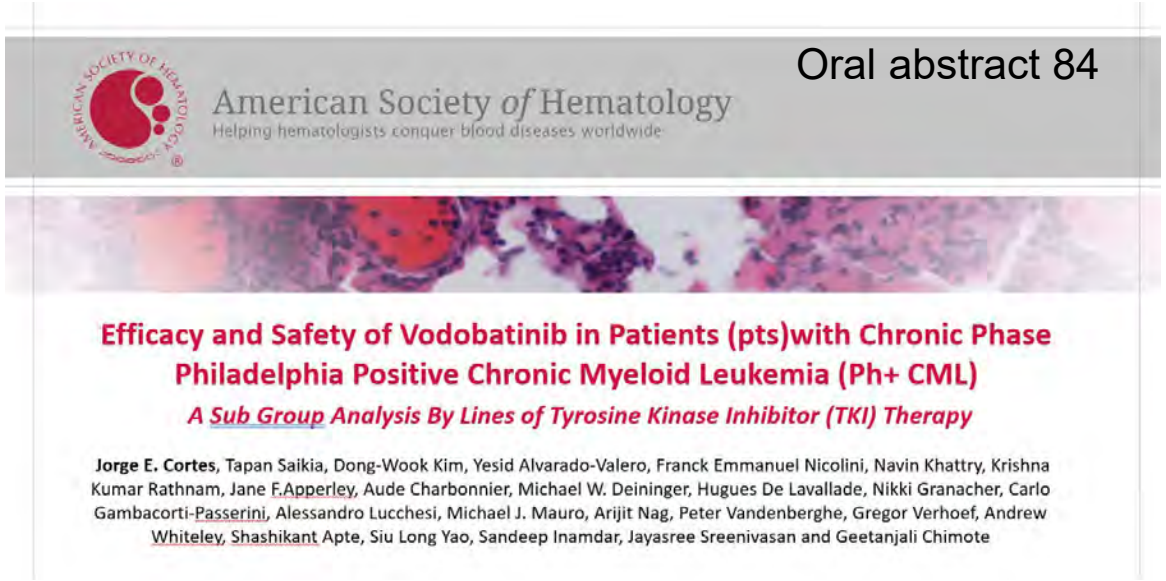
Jabbour E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 82.

Olverembatinib in Resistant CML: Conclusions

- Approximately dose-proportional increase in systemic exposure from 30 to 50 mg QOD; comparable plasma exposure and similar PK profile between China and US patient population
- Efficacy in patients with refractory CML-CP, advanced Ph^+ leukemia, and/or *T315I* mutations
- Strong efficacy in CML patients with resistance or intolerance to ponatinib
- Safe and well tolerated up to 50 mg QOD

Jabbour E et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 82.

Additional abstracts of interest: later line

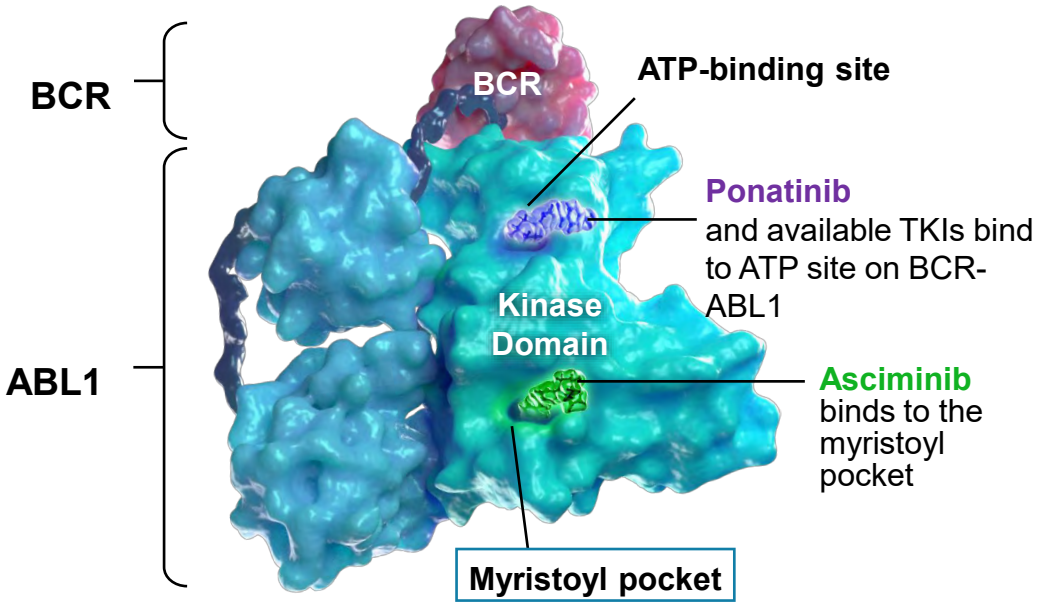


- Vodobatinib is a selective oral inhibitor of *BCR-ABL1.* It is not effective against T315I mutated CML.
- Well tolerated with durable efficacy and safety in CML, including in patients with failure/intolerance to ≥ 3 prior therapies including ponatinib.

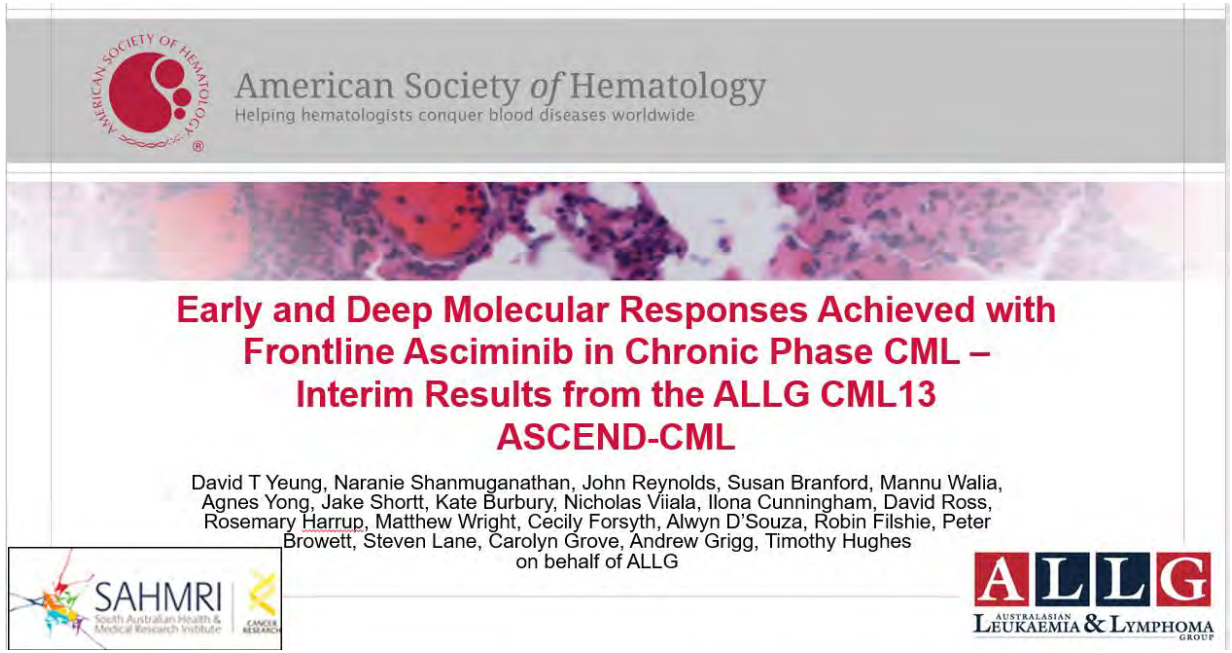
Cortes JE et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 84.

Asciminib in CP CML

2. New therapeutics front-line



Asciminib has been designated as the first-in-class STAMP (**S**pecifically **T**argeting the **A**BL1 **M**yristoyl **P**ocket) inhibitor



- FDA approved ≥ 3rd line at 40 mg BID or 80 mg daily based on the Phase 3 ASCEMBL study, which demonstrated a superior MMR rate at 24 weeks vs bosutinib (primary endpoint) and higher cumulative incidence of *BCR-ABL1*^{IS} ≤ 0.1%: 48 and 96 weeks.
- FDA approved for T315I mutated CML at 200 mg BID

Hughes TP et al. N Engl J Med 2019;381:2315-26.
Réa D, et al. Blood. 2021;138(21):2031-2041.
Mauro M et al. *2022 ASH Annual Meeting.* Abstract 310.
Réa D, et al. 2022 *ASCO Annual Meeting.* Abstract 7004

ASCEND-CML Study design

US Study planned front-line through the Cure CML Consortium

- Newly diagnosed CP-CML
- 100 patients, from 14 Australian and New Zealand sites over 24 months
- Co-primary endpoints
  - EMR, *BCR::ABL1* ≤ 10% at 3 months
  - MMR, *BCR::ABL1* ≤ 0.1% at 12 months
- For patients with poor response to asciminib allowed for the addition of nilotinib, dasatinib or imatinib
  - *BCR::ABL1* > 10% at 3 or 6 months and *BCR::ABL1* > 1% at 12 or 18 months

- *BCR::ABL1* ≤ 10% at 3 months, 92%
- *BCR::ABL1* ≤ 1% at 3 months, 84%
- *BCR::ABL1* ≤ 0.1% at 3 months, 47%
- *BCR::ABL1* ≤ 0.01% at 3 months, 13%

Yeung D et al. Annual American Society of Hematology Meeting, December 2022. Oral abstract 79.

Fred Hutch
Cancer Center

Thank you!

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