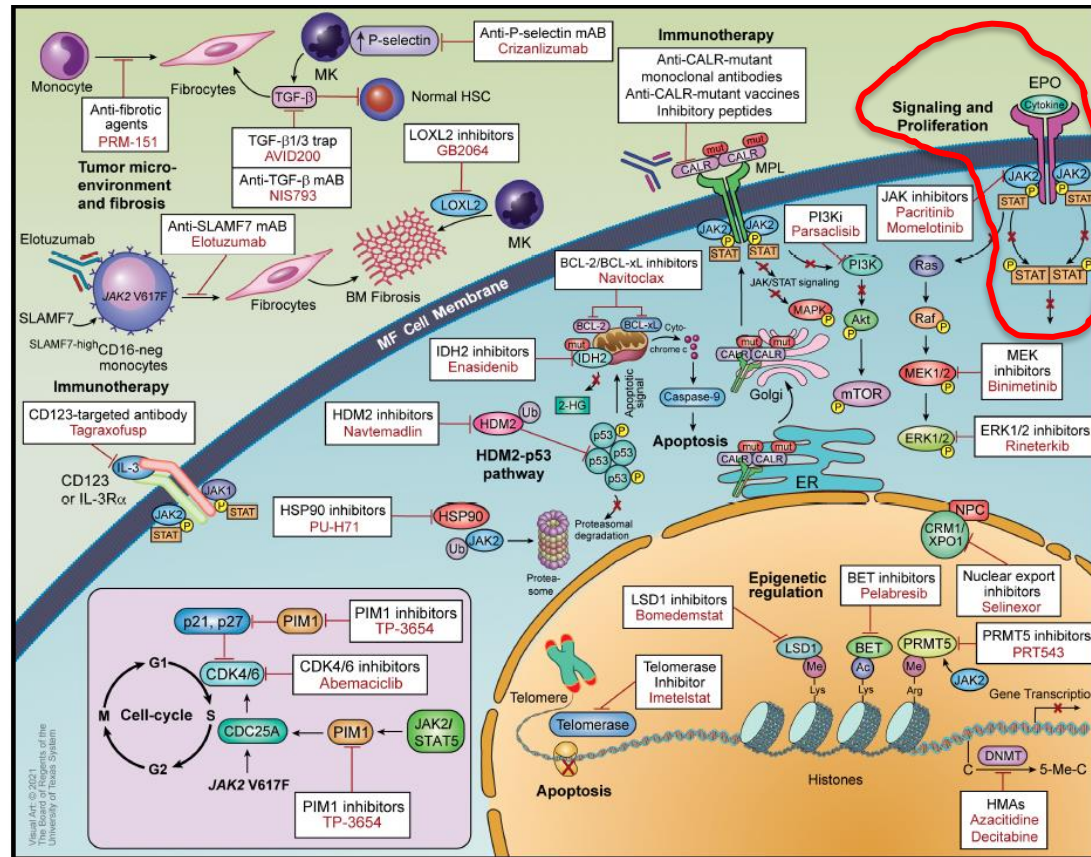


Prospettive future per la terapia del paziente con mielofibrosi

Alessandro M. Vannucchi

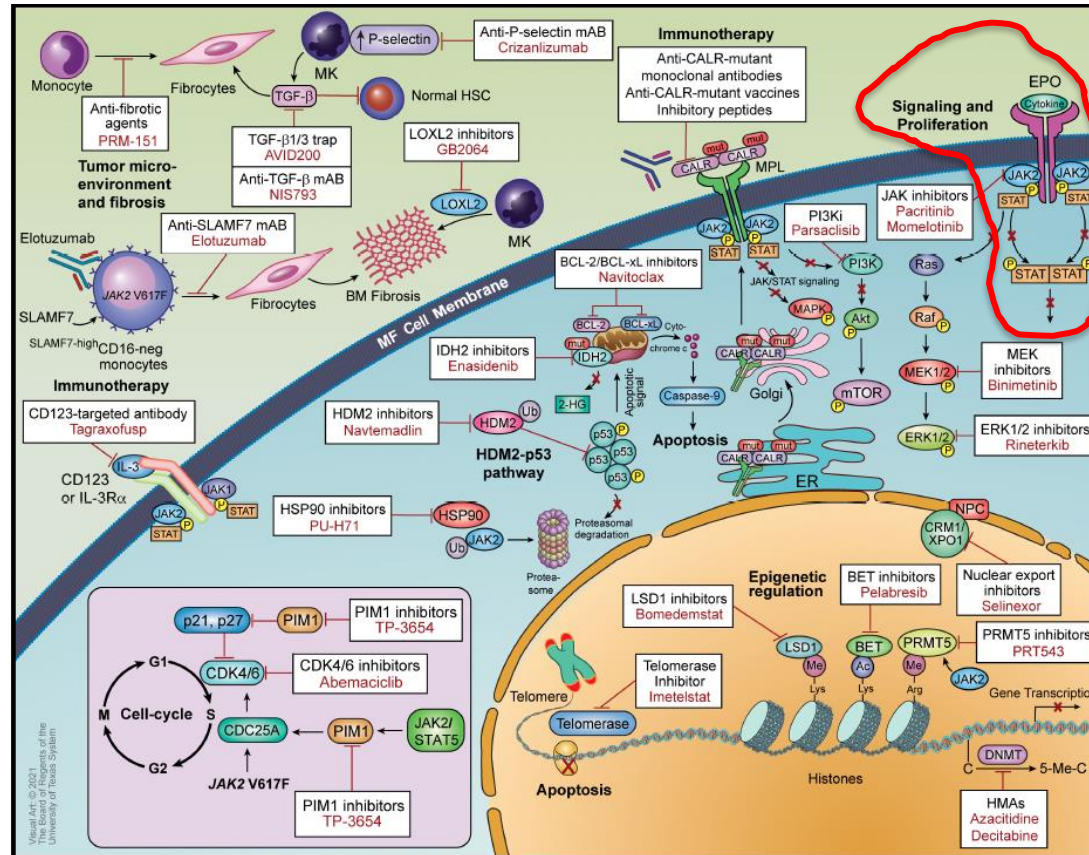
Targets for Treatment in Myelofibrosis, Beyond JAK/STAT



Targets for Treatment in Myelofibrosis, Beyond JAK/STAT

Others non-cell intrinsic

- Anti-fibrotic
- Anti-cytokines



An Unfair Comparison

CML <----- TKi



MF ←-----JAKi



>90% paz have clinical and hematologic response	<50% have clinical and hematologic response
>90% paz have major molecular response	<20% paz has «some» degree of molecular response
<10% paz relapse (clinical/hemato/molec)	>50% relapse at 3-5 years (clinical/hematol)
Usually modest toxicity	Hematologic, immunologic, 2° cancers <i>etc</i> complications
<5% evolve to BP	Approx 20% evolve to BP
OS not very far from normal population	Median OS approx 7y (wide intervals)

Why new therapies??

- To raise % of pts showing clinical and hematologic response
- To reduce % of pts who relapse
- To raise % of pts with *meaningful* molecular response
- To improve clinical/hemato response without increasing AE rate
- To reduce % of BP evolution
- To prolong lifespan
- *etc*

Investigational non-JAK inhibitors in phase III development

In treatment naïve patients

+ ruxolitinib

Pelabresib – BET inhibitor (MANIFEST-2; NCT04603495)

Navitoclax – BCL-xL inhibitor (TRANSFORM-1; NCT04472598)

Luspatercept – TGF- β inhibitor (INDEPENDENCE; LTFU; NCT04717414)

Selinexor – Exportin-1 (SENTRY; NCT04562389)

Navtemadlin – HDM2 inhibitor (POIESIS; NCT06479135)

Monotherapy

Bomedemstat – LSD1 inhibitor (NCT06351631)

In R/R MF

Navtemadlin – HDM2 inhibitor (BOREAS; NCT03662126)

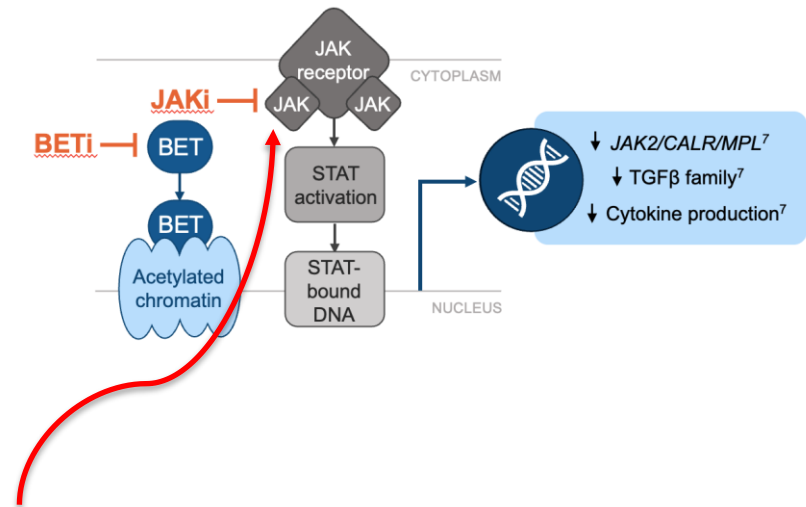
Imetelstat – Telomerase inhibitor (IMpactMF; NCT04576156)

Navitoclax + ruxolitinib – BCL-xL inhibitor (TRANSFORM-2; NCT04468984)

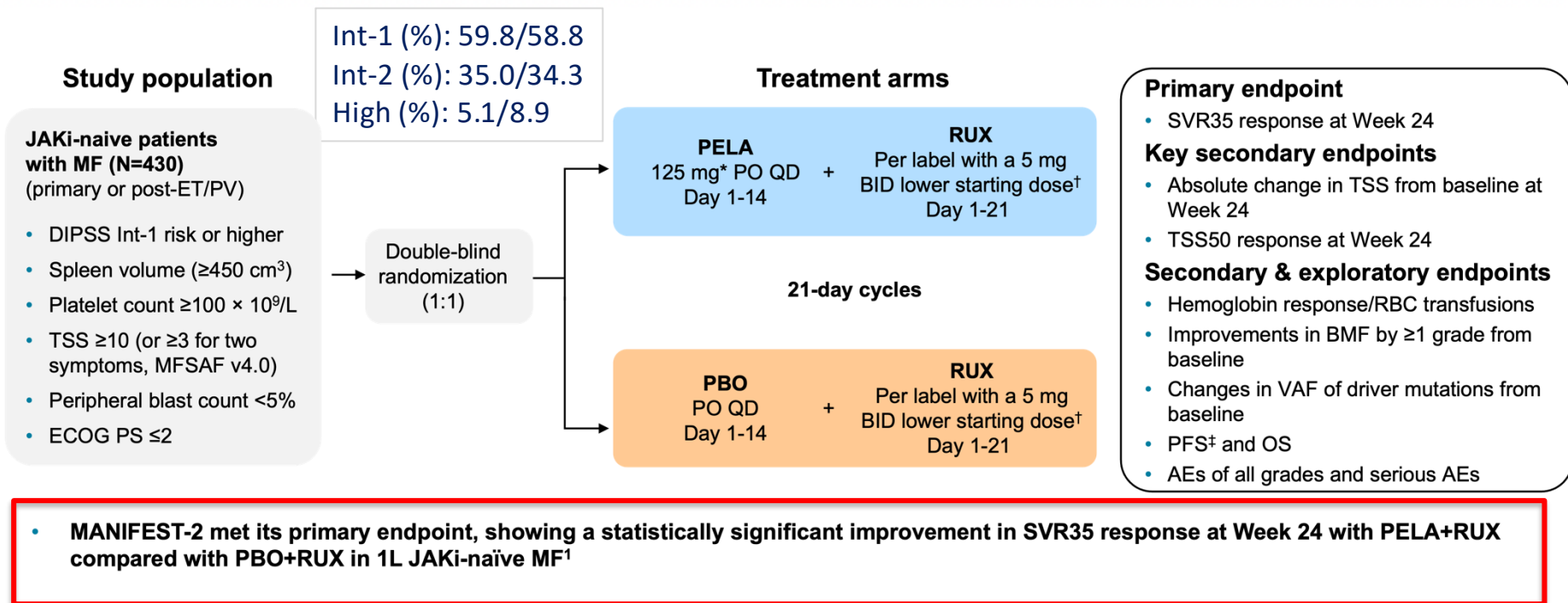


JAK inhibitors combined with BET inhibitors: Rationale

- BET proteins are chromatin-adaptor proteins that bind to acetylated lysines on histones and non-histone proteins via their bromodomains, functioning as co-activators of gene expression at transcriptional start sites and gene enhancers
- In preclinical studies, BET inhibition was shown to:
 1. Downregulate pro-inflammatory cytokines through its effects on the NF- κ B pathway and inhibit megakaryocyte differentiation
 2. Combined with ruxolitinib, to achieve a synergistic reduction of splenomegaly, BM fibrosis and mutant allele burden in a mouse MF model.



Global, randomized, double-blind, active-control, Phase 3 study

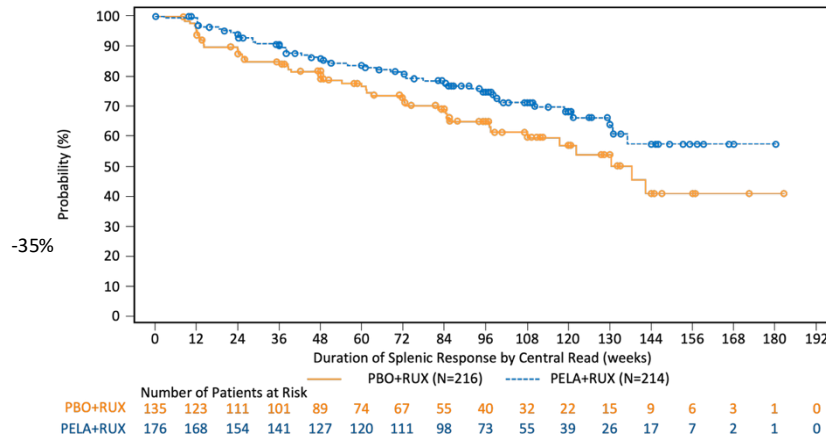
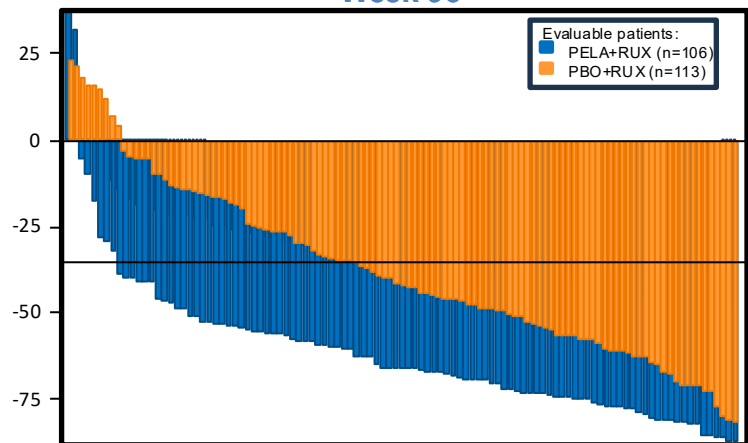


* The starting dose for pelabresib was 125 mg QD and protocol-defined dose modifications based on AEs and treatment response allowed a dose range between 50 mg and 175 mg QD. † RUX was started at 10 mg BID (baseline platelet count $100\text{-}200 \times 10^9/\text{L}$) or 15 mg BID (baseline platelet count $>200 \times 10^9/\text{L}$) with a mandatory dose increase by 5 mg BID after 1 cycle and a maximum dose of 25 mg BID (in case of lack of spleen response) as per the label. RUX dose was comparable between treatment arms and between MANIFEST-2 and COMFORT-II studies⁴. ‡ Defined as the time from randomization to documented progression, or death from any cause.

48.6% of PELA+RUX and 48.1% of PBO+RUX patients remained on study treatment at the Week 96 data cutoff

Significant reductions in spleen volume persisted from Week 24 to Week 96 with PELA+RUX compared with PBO+RUX

Week 96



	PELA+RUX (N=214)	PBO+RUX (N=216)
SVR35 response at Week 96 in evaluable patients	91.5% (97/106)	57.5% (65/113)
Difference	34.0%	
SVR35 response at Week 96 in ITT population	45.3% (97/214)	30.1% (65/216)
Difference† (95% CI)	14.9% (6.1-23.8)	

ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
Median duration of splenic response, weeks	Not reached	138.3
Hazard ratio (95% CI)	0.692 (0.454-1.056)	

Reductions in spleen volume were maintained at Week 96 with PELA+RUX vs PBO+RUX

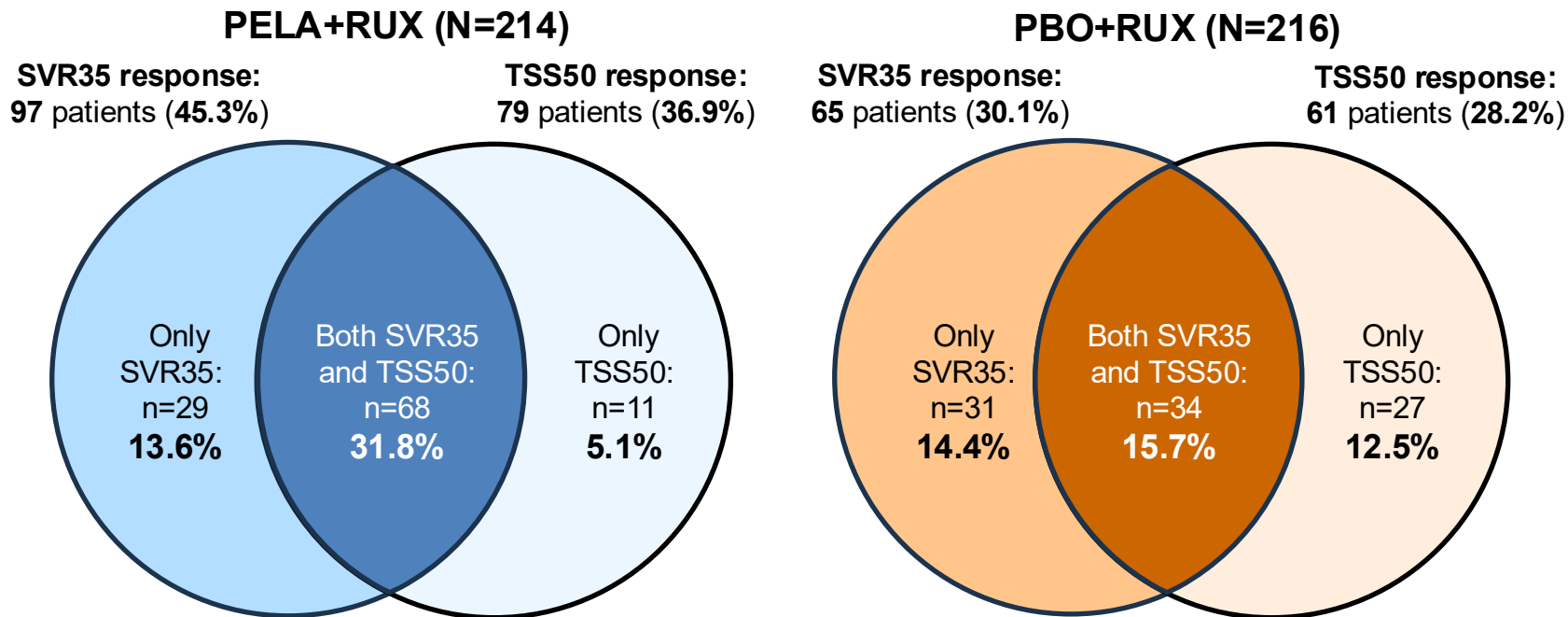
Median duration of splenic response was not reached with PELA+RUX vs PBO+RUX (138w) at Week 96 data cutoff

Data cutoff date: March 02, 2025.

Spleen volume assessed by central read.

Waterfall plots represent evaluable patients who have baseline and Week 24 or Week 96 data. † Calculated by stratified Cochran-Mantel-Haenszel test. CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; SVR35, ≥35% reduction in spleen volume from baseline.

Twice as many patients achieved both SVR35 and TSS50 responses with PELA+RUX vs PBO+RUX at Week 96



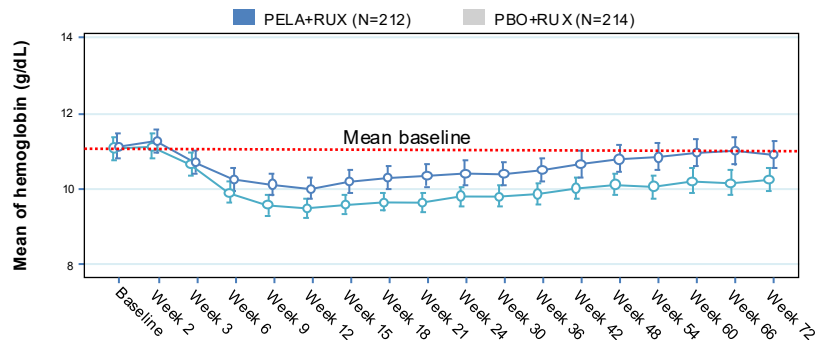
The dual SVR35 and TSS50 response observed with PELA+RUX was maintained from Week 24 to Week 96

Data cutoff date: March 02, 2025.

Analysis is not pre-specified in the study protocol and has been performed post-hoc.

PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; SVR35, $\geq 35\%$ reduction in spleen volume from baseline; TSS50, $\geq 50\%$ reduction from baseline in total symptom score.

Hemoglobin response, and RBC transfusions, with PELA+RUX versus PBO+RUX



Number of at-risk patients

PELA+RUX	212	204	209	199	193	189	186	185	184	181	171	168	162	156	148	144	139	136
PBO+RUX	214	206	211	209	207	205	204	199	196	195	185	179	175	170	161	152	145	139

ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
Hemoglobin response, ^{†,‡} % (n/N) (95% CI)	16.4 (35/214) (11.4-21.31)	9.3 (20/216) (5.39-13.12)
Hemoglobin response, ^{†,‡} in patients with anemia (baseline <10 g/dL), % (n/n) (95% CI)	20.9 (14/67) (11.16-30.63)	16.9 (12/71) (8.18-25.62)

Fewer patients in the PELA+RUX arm versus the PBO+RUX arm required RBC transfusions[§] over 72 weeks:

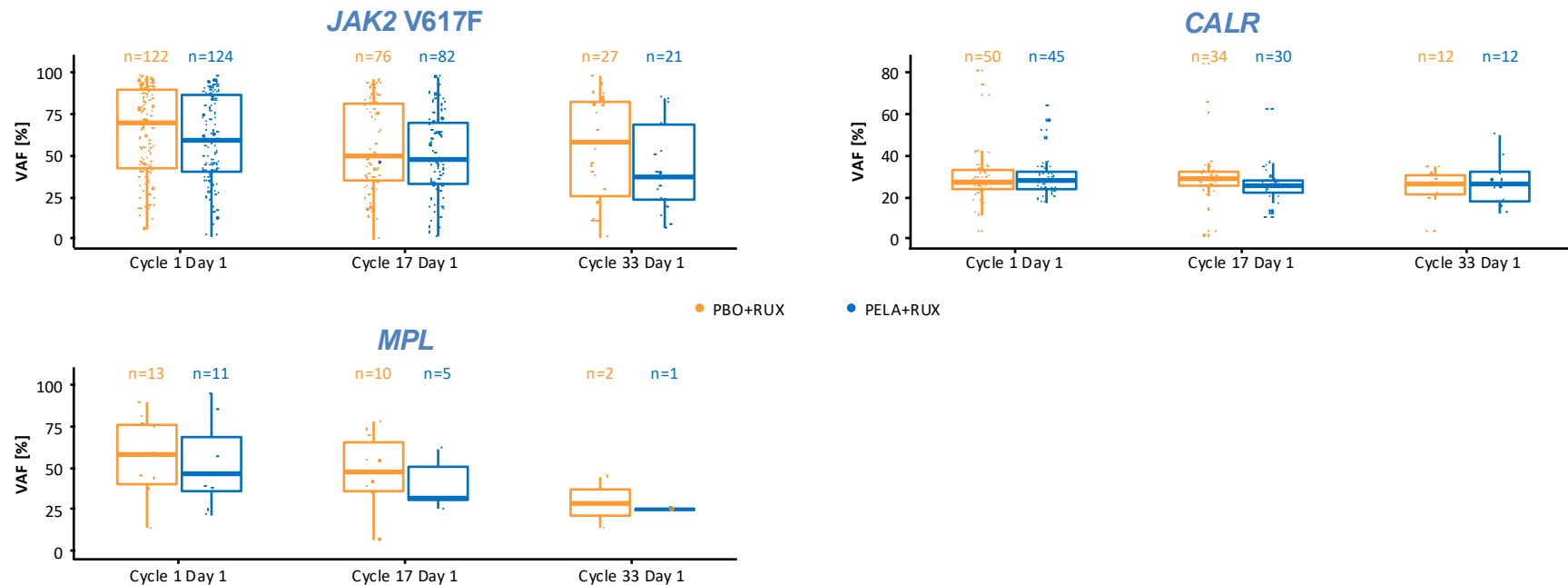
- Weeks 0 to 24: 24.1% (35/145) versus 36.4% (59/162)
- Weeks 25 to 48: 19.3% (28/145) versus 30.9% (50/162)
- Weeks 49 to 72: 19.3% (28/145) versus 25.3% (41/162)

Data cutoff date: August 30, 2024. *Safety population received ≥1 dose of study drug. [†]Hemoglobin response is defined as a ≥1.5 g/dL mean increase in hemoglobin from baseline in the absence of transfusions during the prior 12 weeks in the ITT population.

[‡]Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. [§]RBC transfusions refer to number of patients who received any RBC transfusion during the first 24 weeks after Cycle 1 Day 1, during the 25-48 weeks after Cycle 1 Day 1 or during the 49-72 weeks after Cycle 1 Day 1.

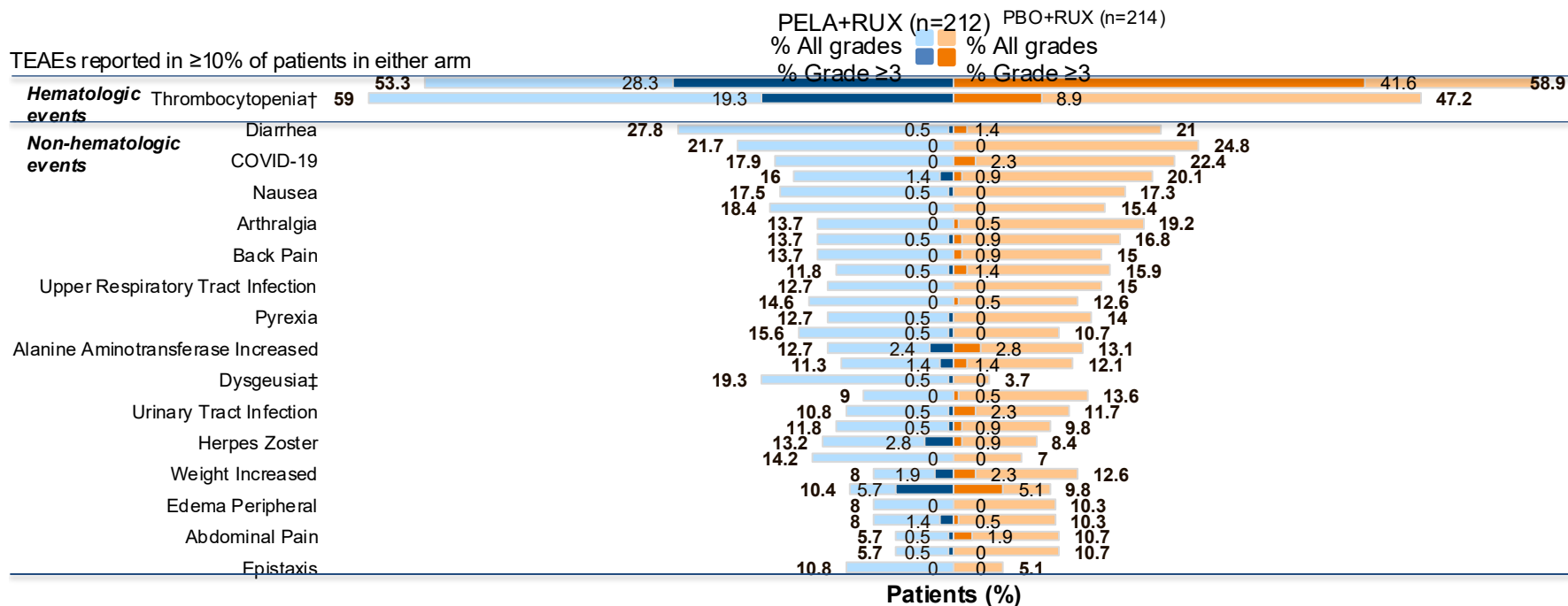
CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RBC, red blood cell; RUX, ruxolitinib.

Reductions seen in MF driver genes at the Week 96 data cutoff with PELA+RUX and PBO+RUX



Reduction in the VAF of *JAK2 V617F*, *CALR* and *MPL* was observed with PELA+RUX and PBO+RUX

Treatment-emergent adverse events were similar between treatment arms at the Week 96 data cutoff



The majority of TEAEs in both treatment arms were low-grade (Grade ≤2)

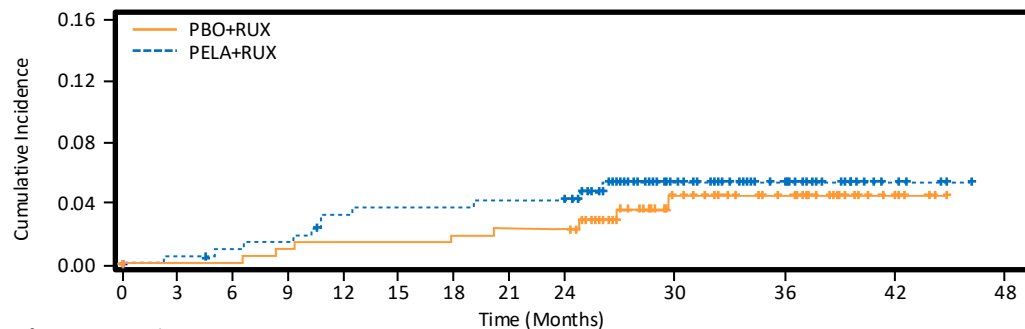
Data cutoff date: March 02, 2025.

AEs are coded using the MedDRA dictionary Version 26.0. A TEAE for the double-blinded treatment period is defined as an AE that has a start date on or after the first dose of the pelabresib/placebo and before 30 days after the last dose of pelabresib/placebo or before the start of alternative (off-study) treatment for MF, whichever occurs first. * 'Anemia' includes preferred terms of anemia and hemoglobin decrease. † 'Thrombocytopenia' includes preferred terms of thrombocytopenia and platelet count decrease. ‡ Dysgeusia was successfully managed in most patients by dose modifications of pelabresib.

AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; MF, myelofibrosis; TEAE, treatment-emergent adverse event.

Comparable rates of accelerated phase and blast phase progression were observed between treatment arms at the Week 96 data cutoff

- Leukemic transformation cases as of March 2, 2025, Week 96 data cutoff*



	PELA+RUX*	PBO+RUX
Accelerated phase, % (n/N)	2.3 (5/216)	1.9 (4/214)
Blast phase, % (n/N)	5.1 (11/216)	3.7 (8/214)

Number of Patients at Risk

PBO+RUX
PELA+RUX

214 210 204 199 190 183 173 166 160 67 30 6 0
216 203 198 185 173 163 157 152 148 66 28 5 0

- Cases of leukemic transformation have remained stable with PELA+RUX since the Week 48 data cutoff; PBO+RUX cases increased from 0.9% (2/214) at Week 48¹ to 3.7% (8/214) at Week 96
- The early imbalance in leukemic transformation cases decreased over time, and cases of leukemic transformation continue to be in line with the previously observed frequency seen in MF²⁻³
- In MANIFEST⁴, no leukemic transformations were observed in Arm 3, a setting similar to MANIFEST-2, within the first 12 months after start of study treatment
- All leukemic transformation cases were adjudicated by an external medical expert committee

Data cutoff date: March 02, 2025.

Assessment based on local laboratory results, adverse events, and documented disease progression. Leukemic transformation confirmed by a bone marrow blast count of $\geq 20\%$ or a peripheral blood blast content of $\geq 20\%$ associated with an absolute blast count of $\geq 1 \times 10^9/L$ that lasts for ≥ 2 weeks. * Minimum of 96 weeks of leukemia-free survival follow-up. The last adjudication in March 2025, with the cutoff as of March 2, 2025, showed a ratio of 11:8. † The denominator of 216 for PELA+RUX includes 4 patients who crossed over from PBO+RUX.

MF, myelofibrosis; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib.

1. Vannucchi AM, et al. Presented at EHA 2025 [Oral S223]; 2. Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807; 3. Mesa RA, et al. *J Clin Oncol*. 2017;35(34):3844-3850; 4. Mascarenhas J, et al. *J Clin Oncol*. 2023;41(32):4993-5004.

Exportin-1 (XPO1) inhibition may target both JAK/STAT and non-JAK/STAT pathways in MF

Exportin 1 (XPO1) transports proteins and protein-RNA complexes out of the nucleus

Selinexor inhibits XPO1-mediated nuclear cargo protein export that may lead to:

- Increased malignant cell death¹
- Reduced inflammation²
- Apoptosis of *JAK2*-mutated MF CD34+ cells but not healthy donor cells³
- Synergism with ruxolitinib and other therapeutic agents in cell lines with or without *JAK2*^{V617F} and *TP53* mutations⁴

Poster 1792

Lu M, et al. Use of Combination Therapies Including the XPO1 Inhibitor Selinexor Is a Potential Effective Therapeutic Strategy to Treat Myelofibrosis Patients Saturday, December 9, 2023:
6:00 PM–8:00 PM
Halls G–H (San Diego Convention Centre)

JAK/STAT pathway inhibition

- ↓ STAT phosphorylation and protein levels^{5,6}
- ↓ AKT and mTOR^{5,7,8}

NF-κB pathway inhibition

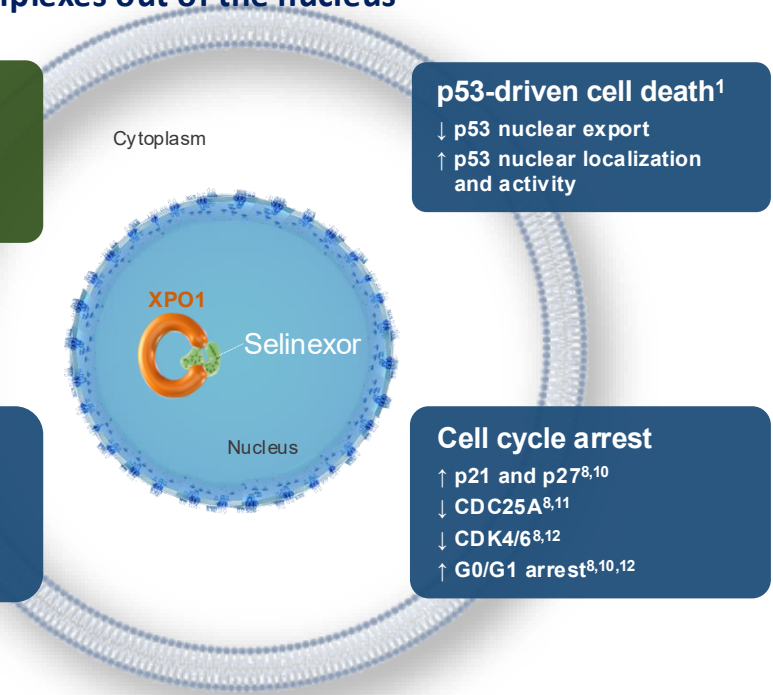
- ↓ IKK phosphorylation²
- ↓ Cytokine production²
- ↑ Nuclear IκBα^{2,8,9}

p53-driven cell death¹

- ↓ p53 nuclear export
- ↑ p53 nuclear localization and activity

Cell cycle arrest

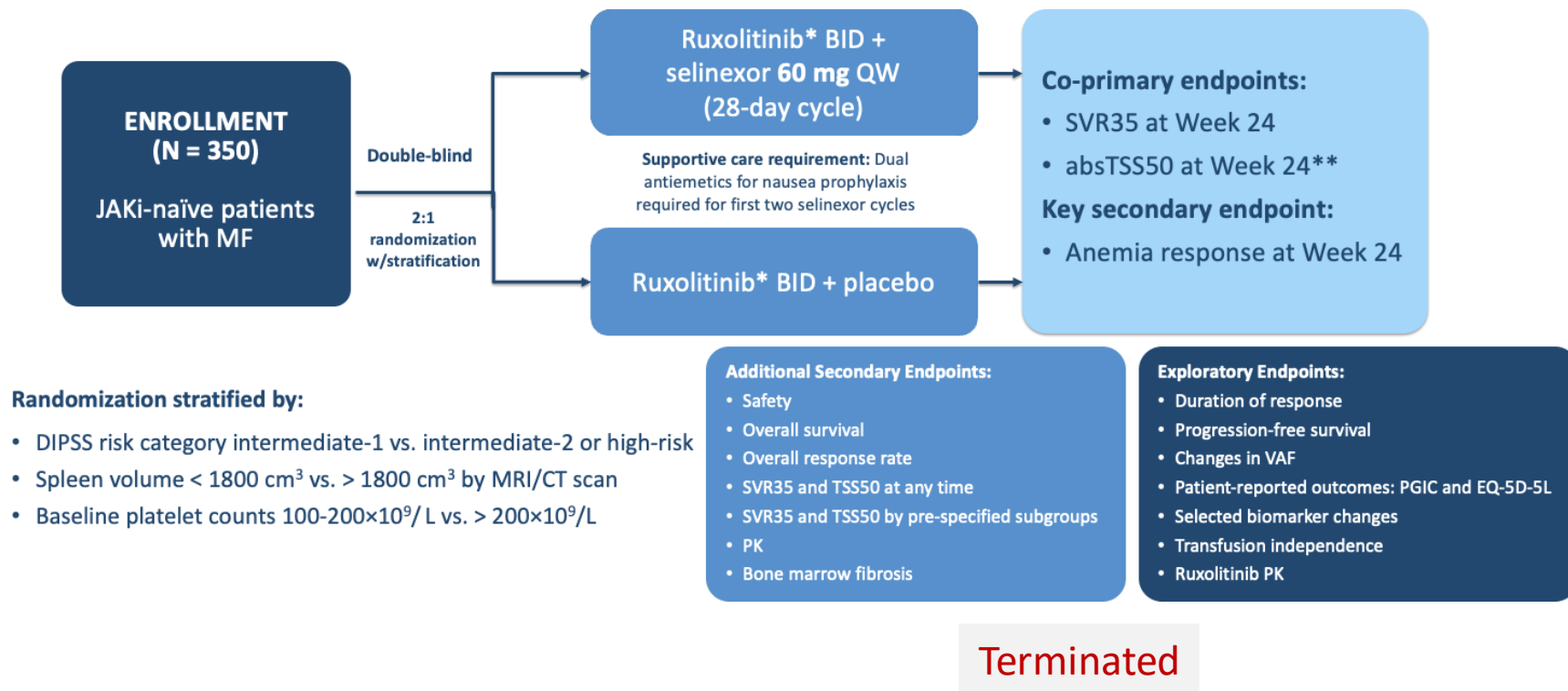
- ↑ p21 and p27^{8,10}
- ↓ CD C25A^{8,11}
- ↓ CD K4/6^{8,12}
- ↑ G0/G1 arrest^{8,10,12}



IκBα, inhibitor of nuclear factor kappa-B kinase subunit alpha; IKK, IκB kinase complex; JAK/STAT, janus kinase/signal transducer and activator of transcription;

MF, myelofibrosis; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; XPO1, exportin 1. 1. Yan D, et al. Clin Cancer Res 2019;25(7):2323–35; 2. Kæhyap T, et al. Oncotarget 2016;7(48):78883–895; 3. Lu M, et al. Poster presented at: 65th ASH Annual Meeting and Exposition; December 9–12, 2023; San Diego, CA. Abstract 1792; 4. Malhotra M, et al. Poster presented at: 15th International Congress for Myeloproliferative Neoplasms (MPN); November 2–3, 2023; Brooklyn, NY; 5. Walker CJ, et al. Blood 2013;122(17):3034–44; 6. Cheng Y, et al. Mol Cancer Ther 2014;13(3):675–86; 7. Argüeta C, et al. Oncotarget 2018;9(39):25529–44; 8. Gandhi UH, et al. Clin Lymphoma Myeloma Leuk 2018;18(5):335–45; 9. Turner JG, et al. Oncotarget 2016;7(48):78896–909; 10. Gravina GL, et al. BMC Cancer 2015;15:941; 11. Garg M, et al. Oncotarget 2017;8(5):7521–32; 12. Tan M, et al. Am J Physiol Renal Physiol 2014;307(11):F1179–86.

Phase 3 Trial Design of Selinexor plus Ruxolitininb for JAKi Naïve Patients with MF (*XPORT-MF-304- SENTRY trial*)

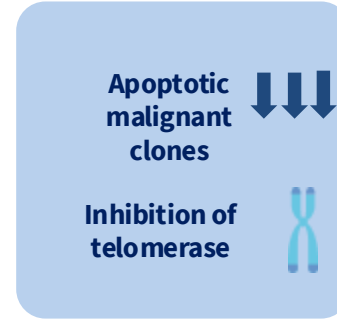
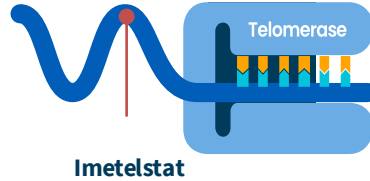
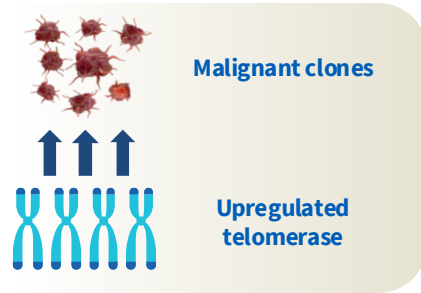


Karyopharm's Phase 3 SENTRY Trial in Myelofibrosis Met First Co-Primary Endpoint, Demonstrating Statistically Significant Improvement in Spleen Volume Reduction

- **SVR35 24w:** 50% combo vs 28% ruxo alone ($p < 0.0001$).
 - SVR35 12w: 49% vs 20%
 - SVR35 36w: 47% vs 23%
 - Post-hoc landmark analysis suggested 12&24w SVR35 predict survival
- **Abs-TSS 24w:** 9.89 points combo vs 10.86 ruxo alone
- **OS:** combo HR 0.43 (95%CI, 0.19-1.00) vs ruxo alone
- **VAF 24w:** a $\geq 20\%$ VAF reduction (*JAK2*, *CALR*, *MPL*) 32% combo vs 24% ruxo alone
- **AE, all-grade:** thrombocytopenia (59% vs 43%); anemia (57% vs 58%), nausea (57% vs 17%), constipation (32% vs 36%), neutropenia (27% vs 9%)
- **AE $G \geq 3$:** 70% vs 50%. **TEAEs leading to treatment discontinuation:** 15% vs 9%.



Telomerases in Cancer Cells and Telomerase Inhibition to Treat Hematological Malignancies



• Telomeres:

- TTAGGG repeats, cap chromosome ends
- Shorten without telomerase
- Accelerated loss under stress

• Telomerase:

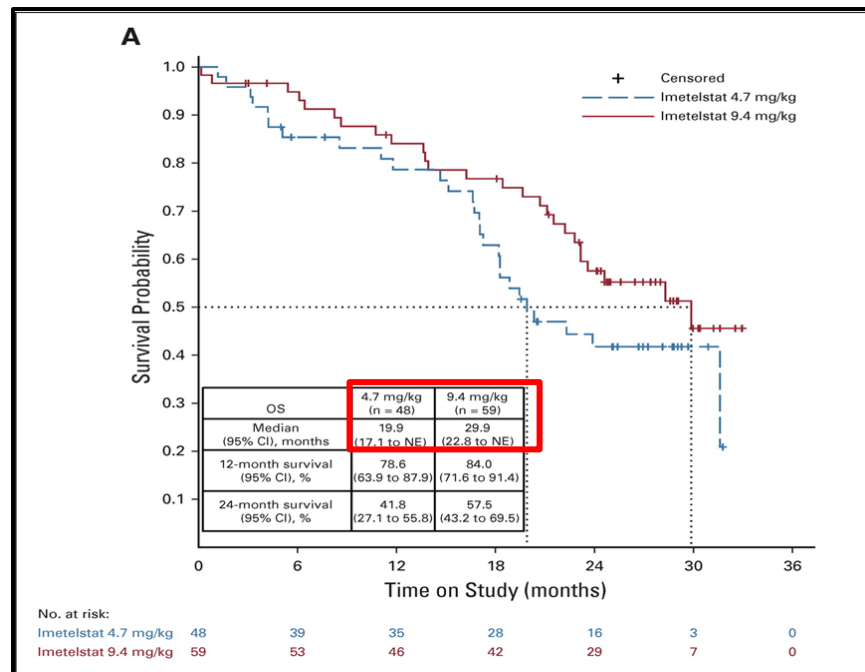
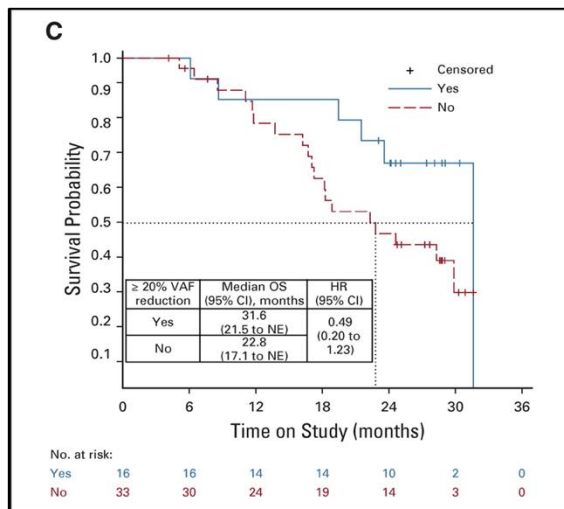
- Synthesizes telomeric DNA
- Not/poorly active in normal somatic cells; transiently upregulated in normal hematopoietic progenitor cells
- Highly upregulated in malignant stem/progenitor cells, enabling continued and uncontrolled proliferation

Imetelstat is approved by the FDA and the European Commission for:

- adult patients with LR-MDS with RBC-TD who are ineligible for ESAs or have relapsed or refractory/unsatisfactory response to ESAs
- It also received FDA and EU Orphan Drug designation, and FDA-Fast Track, for patients with Intermediate-2 and high risk myelofibrosis.

Imetelstat for Myelofibrosis: Phase II study

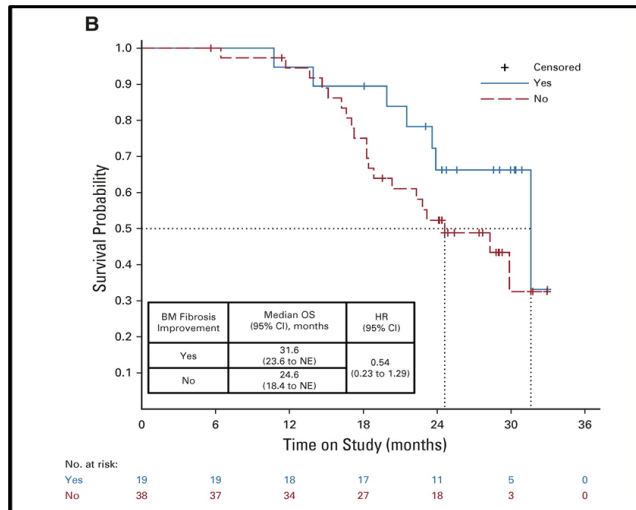
≥20% VAF reduction



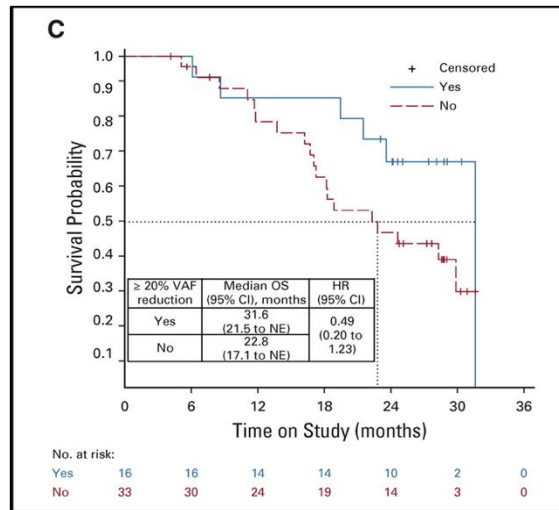
- All liver toxicities were reported as special events and evaluated by an independent Expert Committee
- Six patients experienced grade ≥3 AF, bilirubin, or AST and none deemed related to therapy

Imetelstat for Myelofibrosis

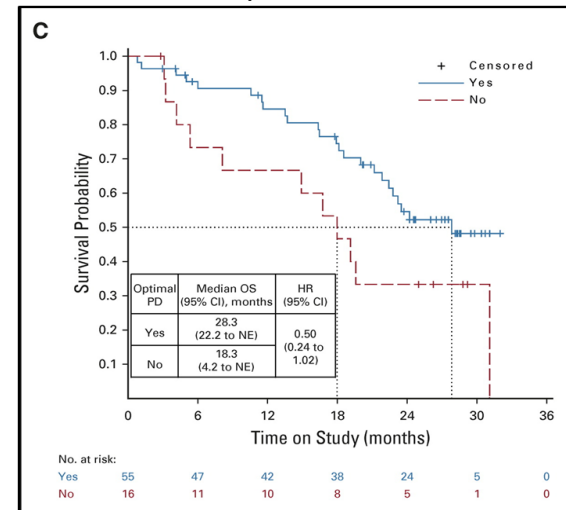
BM fibrosis improvement



≥20% VAF reduction



Optimal PD



Imetelstat 4.7 mg/kg (n = 48)

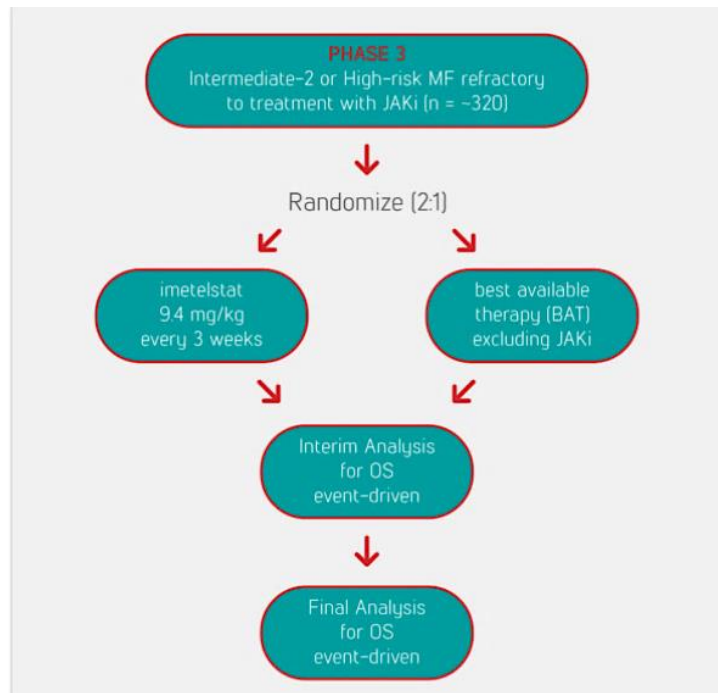
Imetelstat 9.4 mg/kg (n = 59)

Adverse Event	All Grades, No. (%)	Grade ≥ 3, No. (%)	All Grades, No. (%)	Grade ≥ 3, No. (%)
Hematologic (≥ 15% in either arm)				
Thrombocytopenia	11 (23)	11 (23)	29 (49)	24 (41)
Anemia	15 (31)	15 (31)	26 (44)	23 (39)
Neutropenia	5 (10)	5 (10)	21 (36)	19 (32)

- All liver toxicities were reported as special events and evaluated by an independent Expert Committee
- Six patients experienced grade ≥3 AF, bilirubin, or AST and none deemed related to therapy

Imetelstat in R/R Myelofibrosis, Phase III IMpactMF ongoing trial

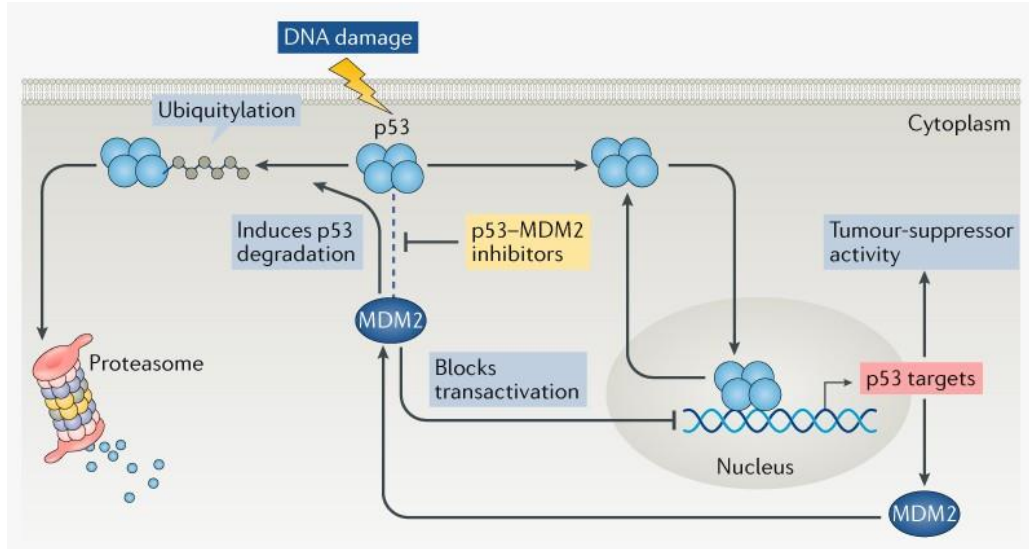
A Study Comparing Imetelstat Versus Best Available Therapy for the Treatment of Intermediate-2 or High-risk Myelofibrosis (MF) Who Have Not Responded to Janus Kinase (JAK)-Inhibitor Treatment - **NCT04576156**



- The **primary “ambitious” efficacy endpoint** for the trial is overall survival (OS).
- **Secondary endpoints** include symptom response, spleen response, progression free survival, duration of response, safety, pharmacokinetics, and patient reported outcomes.
- The final analysis for OS is planned to be conducted after more than 50% of the total enrolled patients have died.

Enrollment completed

MDM2 inhibitor in MF: KRT-232/Navtemadlin



- MDM2 is a key regulator of p53, inhibiting its activity via ubiquitination, nuclear export, and direct inhibition of transcriptional activity.
- Increased MDM2 protein expression has been observed in MF CD34+ cells, suggesting that MF might be sensitive to MDM2 inhibition (Lu M, *Blood*. 2017).
- KRT-232 is a potent and selective, oral, small molecule drug that targets MDM2 and prevents MDM2-mediated p53 inhibition (p53 wild type cells), allowing p53 to mediate tumor cell-cycle arrest and apoptosis.

A Randomized Open-Label Phase 3 Study of Navtemadlin in $TP53^{WT}$ Subjects With Myelofibrosis Who Are Relapsed or Refractory to JAK Inhibitor Treatment

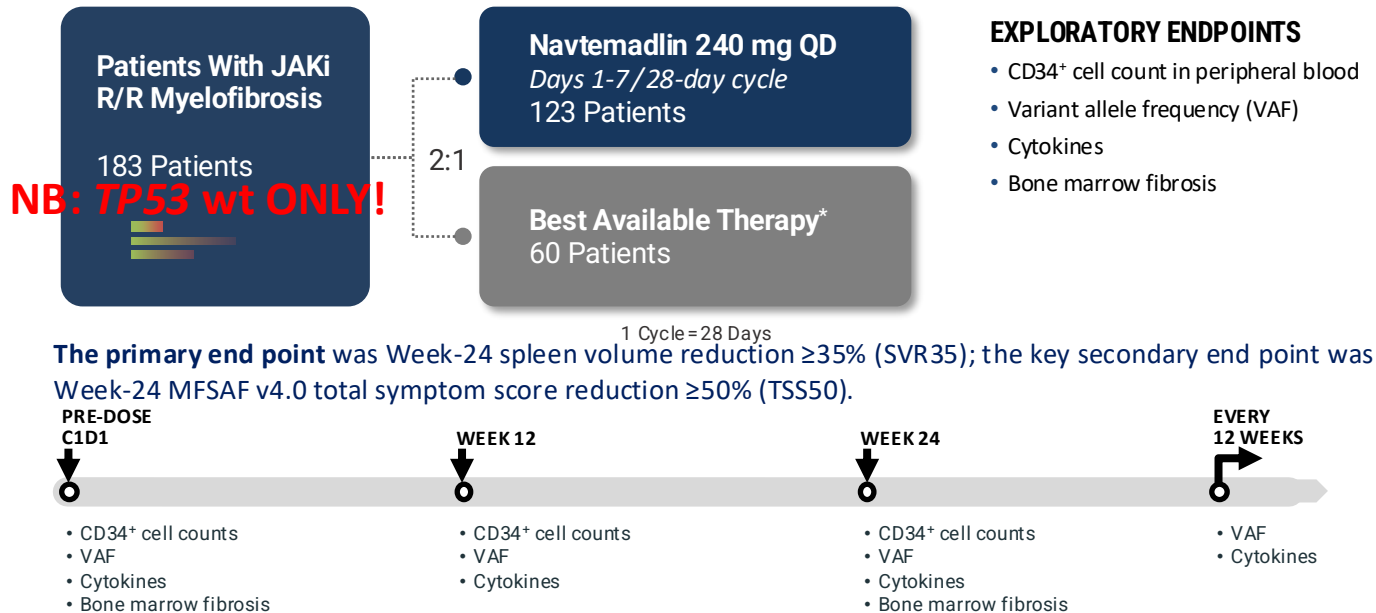


Stratification Factors:

- Primary MF vs Secondary MF
- Baseline TSS (≤ 10 vs > 10)

Physician's Choice (BAT):

- Hydroxyurea
- Chemotherapy
- Peg Interferon
- IMiDs

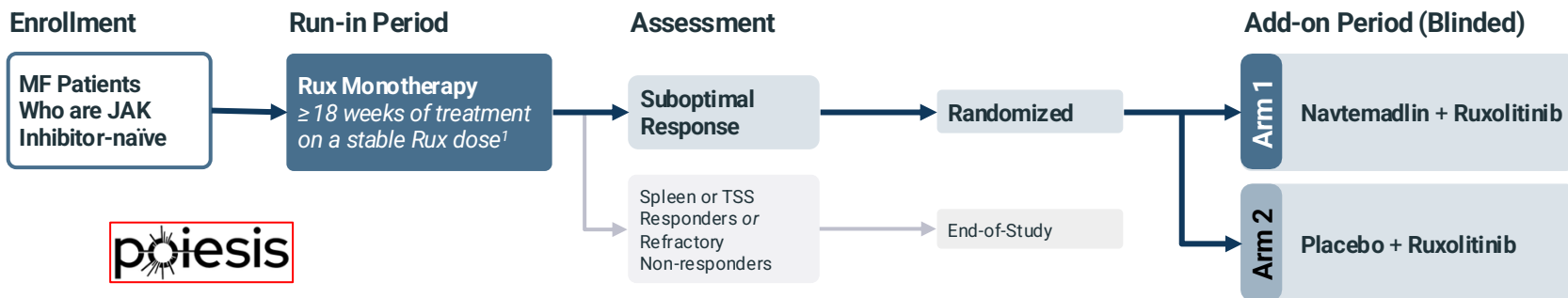


Note: BOREAS enrollment was closed at 183 patients.

*Crossover permitted in the BAT arm after disease progression or at Week 24.

Abbreviations: BAT, best available therapy; C1D1, cycle 1 day 1; IMiDs, immunomodulatory imide drugs (lenalidomide, pomalidomide); JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; QD, once daily; R/R, relapsed/refractory; TSS, total symptom score; VAF, variant allele frequency; WT, wild-type.

A Phase 3 Randomized, Double-Blind, Add-On Study Evaluating Safety and Efficacy of Navtemadlin and Ruxolitinib vs Placebo and Ruxolitinib in JAK Inhibitor-Naïve Patients With Myelofibrosis Who Have a Suboptimal Response to Ruxolitinib



Run-in Period

Key Inclusion Criteria

- Primary or secondary MF by WHO criteria
- Int-1, Int-2, or High-risk disease by IPSS
- Spleen volume $\geq 450 \text{ cm}^3$
- Platelet count $\geq 100 \times 10^9/\text{L}$

Add-on Period

Key Inclusion Criteria

- $TP53^{\text{WT}}$ by central testing
- Treatment with a stable dose of Rux
- Suboptimal response to Rux run-in

Endpoints

Co-primary Endpoints

- Targeted SVR and TSS reduction 24 weeks after randomization

Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle).

¹Stable ruxolitinib is $\geq 5 \text{ mg BID}$ that does not require treatment hold or dose adjustment during the eight weeks prior to add-on navtemadlin or placebo.

Abbreviations: BID, twice daily; Int, intermediate; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; Rux, ruxolitinib; TSS, total symptom score; WHO, World Health Organization; WT, wild-type.

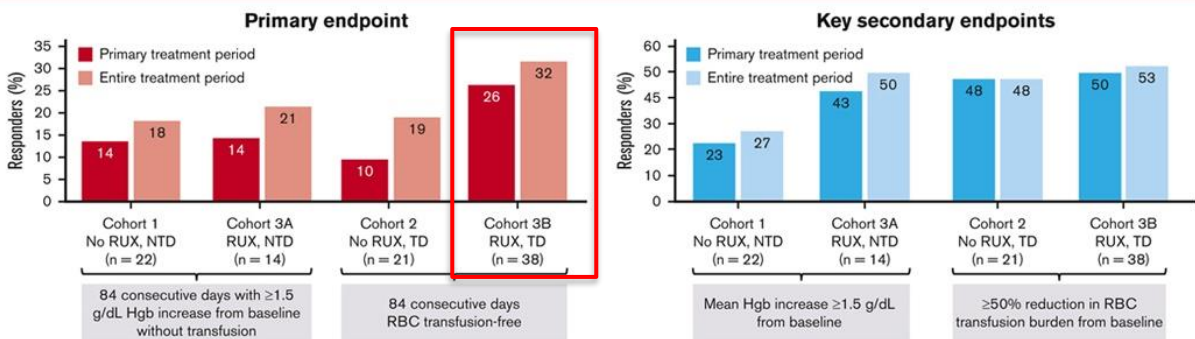
Safety and efficacy of luspatercept for the treatment of anemia in MF

Safety and efficacy of luspatercept for the treatment of anemia in patients with myelofibrosis (MF)

ACE-536-MF-001 (NCT03194542) is a phase 2, multicenter, open-label study



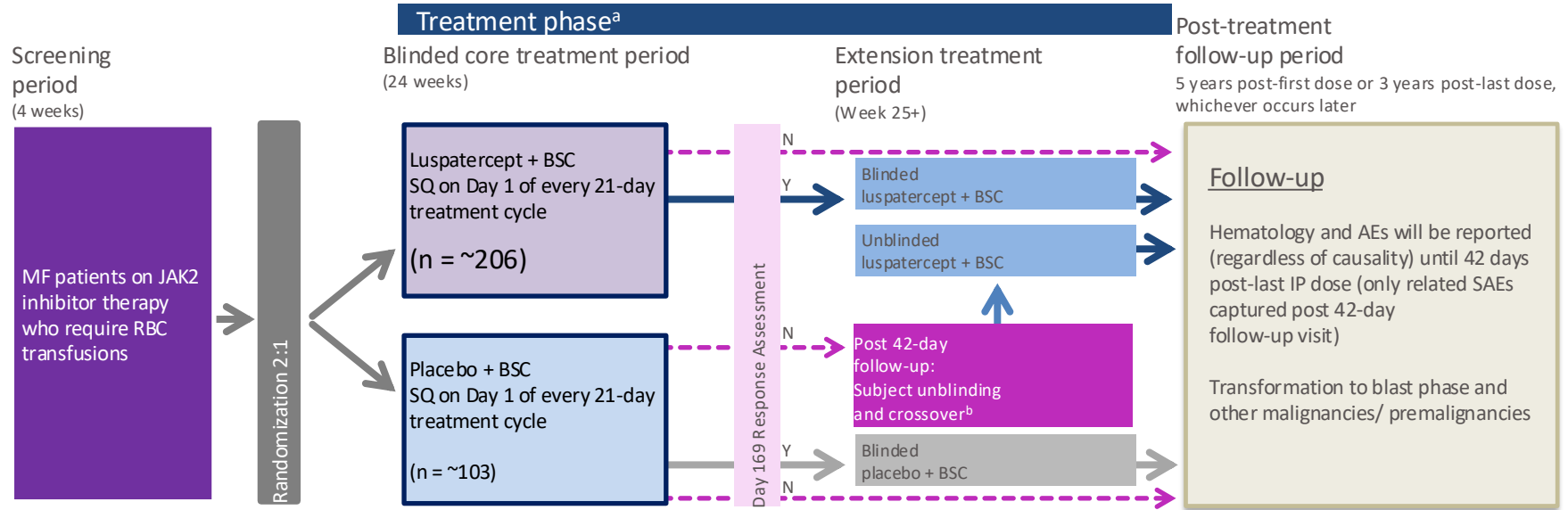
*A stable daily dose of ruxolitinib for ≥ 16 weeks at enrollment; for patients enrolled in expansion cohort 3B, patients had received ruxolitinib treatment per local standard of care for 40 weeks (without interruptions ≥ 2 consecutive weeks) and a stable ruxolitinib dose for 16 weeks at enrollment. [‡]4-12 units/84 days. [†]Including patients enrolled in the expansion cohort. D169, day 169; RBC, red blood cell; RUX, ruxolitinib.



Hgb, hemoglobin; NTD, non-transfusion dependent; RBC, red blood cell; RUX, ruxolitinib; TD, transfusion-dependent.

- Luspatercept improved anemia in transfusion-dependent and non-transfusion-dependent patients with MF, particularly in patients who received concomitant ruxolitinib
- Luspatercept safety profile was consistent with previous studies; no new safety signals were identified

Luspatercept: *INDEPENDENCE* Phase 3, Double-blind, Randomized Study



^a Study unblinding will occur after analysis of the primary endpoint and with DMC consultation; ^b **Subjects who do not meet any of the clinical benefit criteria (defined in the Day 169 Response Assessment as “no”) will have the option to unblind. If the subject is on placebo, they may crossover into the Open-label Extension Treatment Period** and have the opportunity to receive luspatercept after meeting the safety-related eligibility criteria (all inclusion and exclusion criteria are met except inclusion criteria 1 through 4). Unblinding can only occur after completion of the Day 169 Response Assessment, EOT visit, and 42-day Follow-up Period. Those subjects on placebo have the opportunity to receive luspatercept treatment and be treated for at least 24 weeks in the Open-label Extension Treatment Period as long as they continue to demonstrate clinical benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation. AE, adverse event; BSC, best supportive care;



July 18, 2025

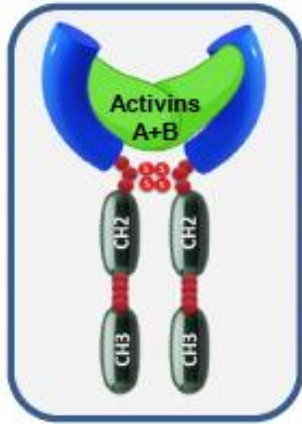
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Bristol Myers Squibb Announces Topline Results from Phase 3 INDEPENDENCE Trial for Reblozyl® (luspatercept-aamt) in Adult Patients with Myelofibrosis-Associated Anemia

PRINCETON, N.J.--(BUSINESS WIRE)-- [Bristol Myers Squibb](#) (NYSE: BMY) today announced the Phase 3 INDEPENDENCE trial evaluating *Reblozyl*® (luspatercept-aamt) with concomitant janus kinase inhibitor (JAKi) therapy in adult patients with myelofibrosis-associated anemia receiving red blood cell (RBC) transfusions did not meet its primary endpoint of RBC transfusion independence during any consecutive 12-week period, starting within the first 24 weeks of treatment, compared to placebo (p=0.0674). Patients saw a numerical and clinically meaningful improvement in RBC transfusion independence favoring *Reblozyl*, in line with previous results from the Phase 2 trial ([NCT03194542](#)).

Several important secondary measures also showed a clinically meaningful benefit favoring *Reblozyl*, which included a higher number of patients who achieved at least a 50% reduction (and by at least 4 RBC units) in RBC transfusion burden, as well as a higher number of patients achieving a hemoglobin (Hb) level increase by at least 1 g/dL while remaining transfusion independent for at least 12 consecutive weeks.

ELRITERCEPT

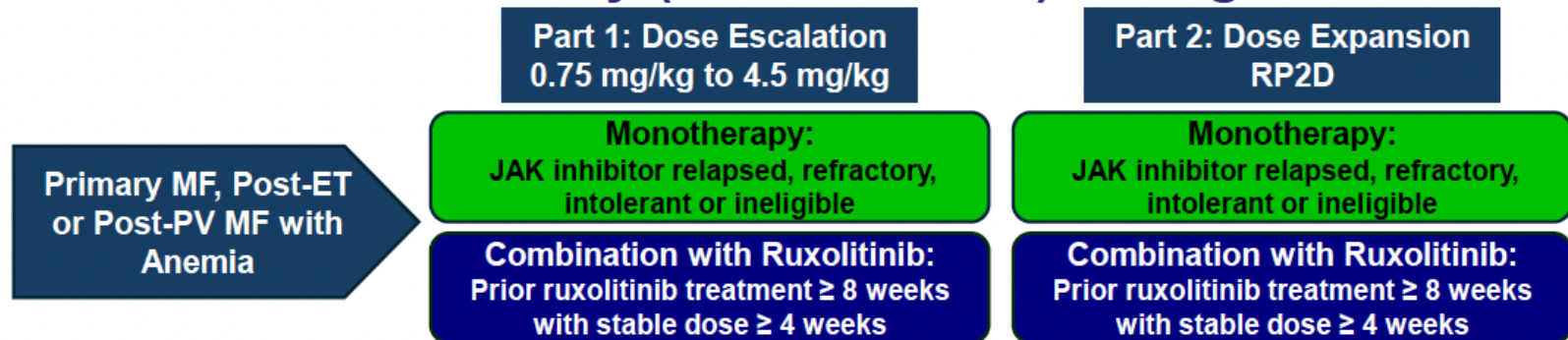


- Designed to inhibit select TGF-beta superfamily ligands, including **Activin A**, which has been associated with **ineffective hematopoiesis, inflammation, disease pathogenesis and progression**^{1,2,3}

Preclinical data showed that the research form of **elritercept** (RKER-050):

- induced erythropoiesis in mouse model of myelofibrosis⁴
- reversed ruxolitinib-associated reductions in hemoglobin, hematocrit, and red blood cell (RBC) count⁵
- increased platelet counts⁶

Phase 2 RESTORE Study (NCT05037760): Design and Status



Key Eligibility

- Transfusion dependent (TD): average of ≥ 6 RBC units/12 weeks with ≥ 1 transfusion within 28 days prior to treatment
- Non-transfusion dependent (Non-TD): baseline hemoglobin < 10 g/dL, with or without transfusions
- Baseline platelet count $\geq 25 \times 10^9/L$

Objectives and Endpoints

- Primary: To evaluate safety and tolerability of elritercept as monotherapy or in combination with ruxolitinib in participants with MF
- Secondary/Exploratory: To evaluate effects of elritercept on anemia, spleen volume, symptom score, exploratory biomarkers

Study Status

- Part 1 Dose Escalation complete
- RP2D* identified as 3.75 mg/kg Q4W with option to up-titrate to 5 mg/kg Q4W
- Part 2 Dose Expansion open and enrolling
- Total of 54 participants enrolled as of data cutoff date

IMMUNOTHERAPY Inca033989, A Mutant CALR Specific Monoclonal Antibody

- INCA033989 has a unique mechanism of action compared with other available therapies
 - INCA033989 is a novel, fully human, high-affinity, Fc-silenced, immunoglobulin G1 monoclonal antibody that selectively targets mutCALR in complex with thrombopoietin receptor to inhibit oncogenic signaling and proliferation of cells¹

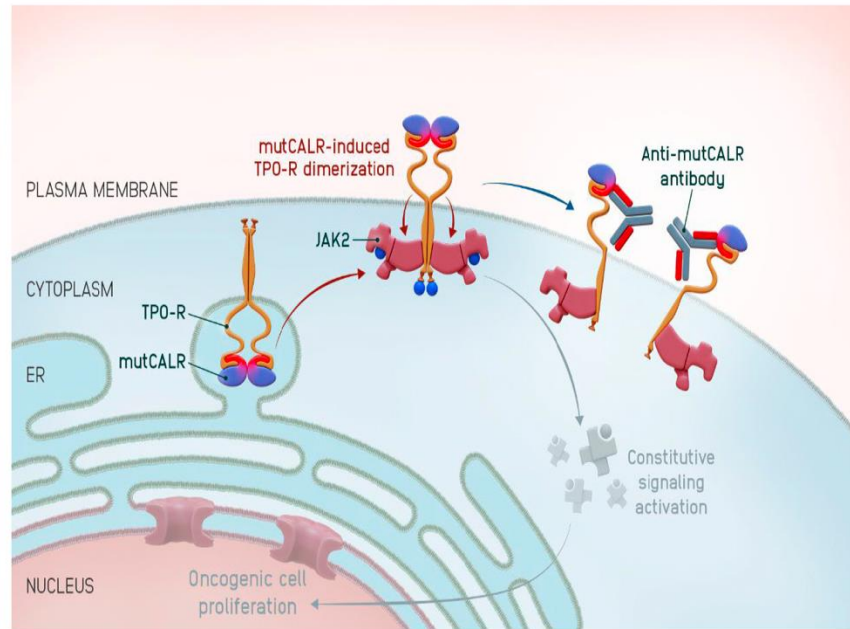
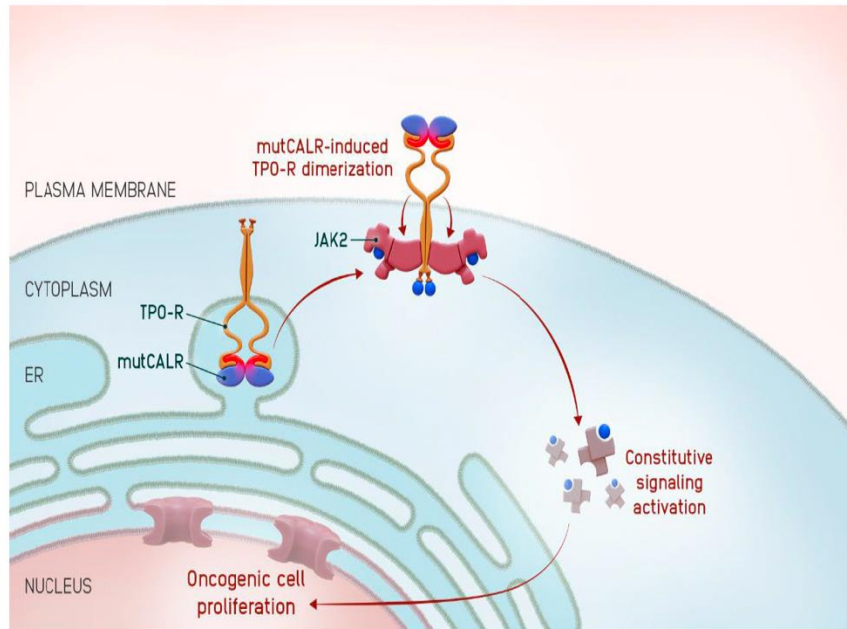


Figure reprinted from Reis E, et al. *Blood*. 2024;144:2336-2348 [visual abstract] with permission of Elsevier Inc. Copyright © 2024 American Society of Hematology.

Two Ongoing Phase 1 Studies Evaluating INCA033989 in Patients With MF and ET

Study Design

Dose Escalation

MF

- ≥18 years of age with a diagnosis of primary or post-ET MF
- Presence of mutCALR exon 9
- Spleen volume imaging ≥450 mL or palpable splenomegaly of ≥5 cm
- Monotherapy
 - Intolerant, resistant after ≥12 weeks, or ineligible for JAKi treatment
- Combination therapy
 - Prior ruxolitinib treatment for ≥12 weeks with a suboptimal response

ET

High risk; documented resistance/intolerance to ≥1 line of prior cytoreductive therapy

Primary Endpoints

- Dose-limiting toxicities
- Treatment-emergent adverse events

Secondary Endpoints

- SVR25 and SVR35 at weeks 12 and 24*
- Anemia response¹
- Symptom improvement based on the MPN-SAF TSS
- Changes in allele burden of mutCALR

Dose Expansion

MF (monotherapy)

MF (INCA033989 + ruxolitinib)

JAKi-naïve MF (randomly assigned to monotherapy or INCA033989 + ruxolitinib)

ET

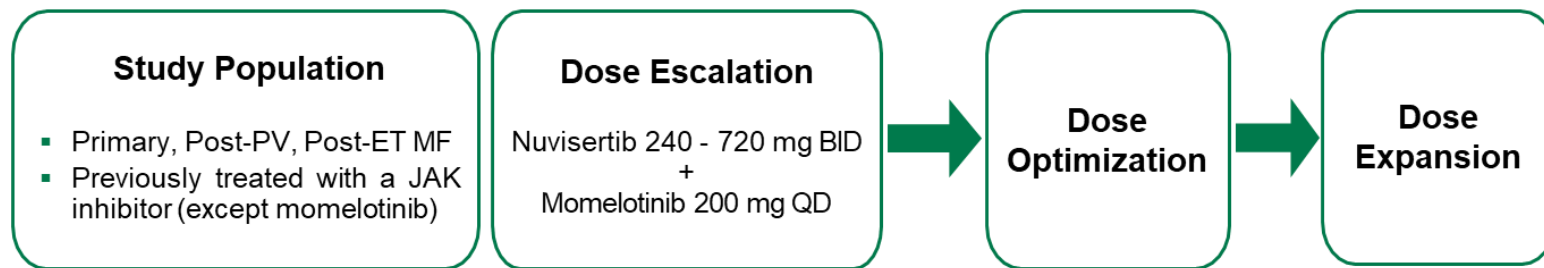
- **INCA033989-101** (NCT05936359; outside the US) and **INCA033989-102** (NCT06034002; US only) are phase 1, first-in-human, multicenter, open-label studies evaluating INCA033989 in patients harboring a CALR exon-9 mutation with high-risk ET or MF (as monotherapy or in combination with ruxolitinib)
- INCA033989 was administered intravenously every 2 weeks (24-2500 mg)

*A spleen response required confirmation by MRI or CT showing SVR25 or SVR35.

1. Tefferi A. *Blood*. 2024;144:1813-1820.

CALR, calreticulin; CT, computed tomography; ET, essential thrombocythemia; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; MRI, magnetic resonance imaging; mutCALR, mutations of calreticulin; SVR25, spleen volume reduction ≥25%; SVR35, spleen volume reduction ≥35%; TSS, total symptom score.

Global Phase I/II Study of Nuvisertib + Mometotinib Combination in MF



Key Eligibility	Endpoints
▪ DIPSS Intermediate- 1, 2, or high-risk ▪ Platelet count $\geq 50 \times 10^9/L$ ▪ Hemoglobin $< 10 \text{ g/dL}$ ▪ ECOG Performance Status ≤ 1 ▪ Splenomegaly ($\geq 450 \text{ cm}^3$ by MRI/CT) ▪ At least 2 symptoms measurable with each score ≥ 3 or a total score of ≥ 10 per MF-SAF v4.0	▪ Primary: • Safety and tolerability ▪ Secondary • Spleen volume reduction (SVR) • Total symptoms score (TSS) reduction • Overall survival • Bone marrow fibrosis change • Pharmacokinetics

NUVISERTIB is an orale selective PIM inhibitor that showed promising preliminary single-agent clinical activity in patients with R/R MF



TRIAL IN PROGRESS: A STUDY OF ROGINOLISIB IN COMBINATION WITH RUXOLITINIB IN PATIENTS WITH MYELOFIBROSIS WHO ARE UNRESPONSIVE TO JAK INHIBITORS (HEMA-MED)

IONCTURA

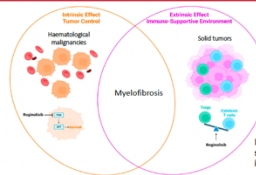
Alessandro Vannucchi¹, Chiara Paoli¹, Paola Guglielmelli¹, Michael Lahn², Giusy Di Conza², Tracey Hammett², Paramjit Kaur², Jasson Villarreal Hernandez³, Mario Tinbelli⁴, Armando Santoro⁵, Matteo Della Porta⁵

¹ CRIMM, Hematology Unit, AOU Careggi, University of Florence, Florence, Italy; ² Ionctura Research and Development, Geneva, Switzerland, Geneva, Switzerland; ³ Hematologia Clinica, Institut Català d'Oncologia-Hospital Duran i Reynals, 08908-L'Hospitalet del Llobregat, Spain; ⁴ Division of Hematology and BMT, Department of Medicine, University of Udine and Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy; ⁵ Cancer Center, IRCCS Humanitas Research Hospital, Milan, Italy, Milan, Italy

BACKGROUND

- Inhibition of both the Phosphoinositide 3-kinase (PI3K) pathway and Janus kinase (JAK) signalling leads to decreased proliferation of cells from patients with myelofibrosis (MF) in clonogenic assays
- Highly selective PI3K δ inhibition results in blocking tumor-cell intrinsic and extrinsic pathways^{1,2,3}
- Roginolisib (formerly IOA-244) has a unique mechanism of action as an allosteric modulator and a highly selective PI3K δ inhibitor⁴
- In its first-in-human (FiH) dose study (NCT04328844), 44 patients (36 with solid tumors and 8 with follicular lymphoma) received roginolisib with no drug-associated, PI3K inhibitor related, toxicities, nor needed dose modifications in the absence of a dose limiting toxicity (DLT)⁵

ROGINOLISIB MECHANISM OF ACTION^{4,8,9,10}



Roginolisib hemi-fumarate at 80 mg QD is determined to be the optimal biologically effective dose based on the phase 1 study (IOA-244-101; NCT04328844)

In a preclinical myelofibrosis model, roginolisib showed efficacy by directly synergizing with JAK2 in patient cells and extrinsically by reducing dysfunctional immune cells (see poster number 5529, session 631-Balliu et al.)

OBJECTIVE: HEMA-MED (NCT NCT06887803) aims to evaluate the safety and tolerability of roginolisib when administered in combination with ruxolitinib in patients with Myelofibrosis

STUDY DESIGN AND METHODS

A prospective, multi-centre, Phase 1/2, single arm open - label study consisting of 2 parts. Part 1 will enroll 13 patients to assess the safety of the combination. Part 2 will expand to add 13 more patients to allow the assessment of benefit/risk for all 26 patients. The dose of roginolisib will be 80 mg IOA-244 QD

KEY ELIGIBILITY CRITERIA

- ≥ 18 years of age inclusive, at the time of signing the informed consent
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
- Diagnosis of primary MF, Post-Polycythemia Vera Myelofibrosis MF (PPV-MF), or post-essential thrombocythemia MF (PET-MF)
- Treated with ruxolitinib for ≥ 3 months with a stable dose ≥ 10 mg for a minimum of 8 weeks prior to Day 1 and an unsatisfactory spleen reduction
- Independent of spleen size, active symptoms of MF at the screening visit, as demonstrated by the presence of a TSS of ≥ 10
- Peripheral blast count $< 10\%$
- No history of prior Grade 3 or 4 AE which did not respond to therapy or not resolved with treatment interruptions and not returned to at least Grade 1

STUDY ENDPOINTS AND ASSESSMENT

Primary: To evaluate the safety and tolerability of roginolisib when administered in combination with ruxolitinib in patients with MF
Secondary: Changes in peripheral blood Tregs from baseline at week 12; Splenic response rate (SRR) at week 12 and 24 compared to baseline; Proportion of patients with reduction in Total Symptom Score (TSS) at week 12 and 24 compared to baseline
Exploratory: Assess endpoints associated with the mechanism of actions of roginolisib including protein expression, Tregs, chemokine and cytokine levels

SUMMARY

- The combination of ruxolitinib and roginolisib is expected to provide a safe combination treatment in patients with MF who have a sub-optimal response to ruxolitinib defined by unsatisfactory reduction in spleen size and/or presence of MF-related symptoms
- Eligible patients are those with MF who have a sub-optimal response to ruxolitinib
- Approximately 26 patients will be enrolled to this study
- The study is actively recruiting and open for enrolment in Italy and Spain. UK sites in start-up.

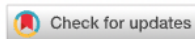
References

¹Ali et al. Nature 2004; 431:1007-11; ²Tarantelli et al. Cancers 2021; 13:5530; ³Holler et al. Cancer Res 2008; 14:1172-81; ⁴MacQueen et al. Cancer Res Commun 2023; 3(1):576-579; ⁵MacQueen et al. AACR Annual Meeting 2024; Poster for Abstract 89507; ⁶MacQueen et al. AACR 2020; Poster for Abstract 666; ⁷Mougiakakos et al. Cancer 2019; 119(9):2224-33; ⁸Qin et al. J Immunother Cancer 2020; 8(2):e000060; ⁹Handberg et al. Cell Death and Dis 2021; 20:1990-2000; ¹⁰Calabro et al. Cancers 2021; 13:4040

Roginolisib is a selective PI3K δ inhibitor, that in preclinical experiments in primary MF cells, especially when combined with JAK2 inhibitors, showed evidence of synergism

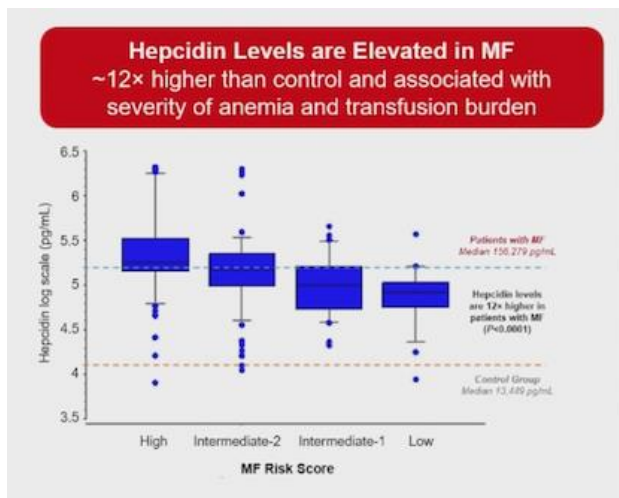
RALLY MF: A phase 2 Study of DISC-0974, an anti-hemojuvelin antibody, in patients with myelofibrosis and anemia

Naseema Gangat, Ayalew Tefferi, Prithviraj Bose, Elizabeth Hexner, Laura Michaelis, Aaron Gerds, Akriti Jain, Prioty Islam, Raajit Rampal, Ronan Swords, Moshe Talpaz, Kristen Pettit, Sima Bhatt, Akshay Buch, Olivia Pelletier, Will Savage, Anna Halpern



Blood (2025) 146 (Supplement 1): 2042.

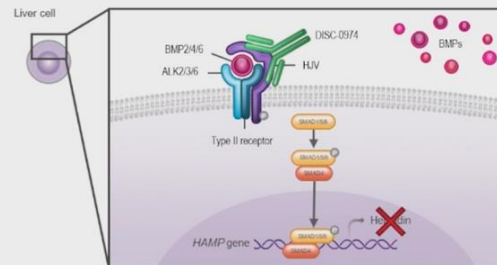
<https://doi.org/10.1182/blood-2025-2042>



DISC-0974 Targets Hemojuvelin (HJV) to Suppress Hepcidin

Inhibiting HJV Prevents Hepcidin Expression and Increases Iron

- **DISC-0974** is a first-in-class monoclonal antibody that binds to HJV and blocks BMP signaling
- ↓ Hepcidin production
- ↑ Iron absorption
- ↑ Mobilization of stored iron into circulation
- ↑ Hgb levels





Strategie condivise
per la Mielofibrosi

29 aprile 2026 • Firenze

Prospettive future per la terapia del paziente con mielofibrosi

Alessandro M. Vannucchi