Imperial College London

NHS
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New Therapies Development in Myelofibrosis

Dr Andrew Innes
Consultant Haematologist
Clinical Senior Lecturer
Hammersmith Hospital and Imperial College London

Disclosures

- Speakers bureau: Incyte and Novartis
- Advisory board: Novartis

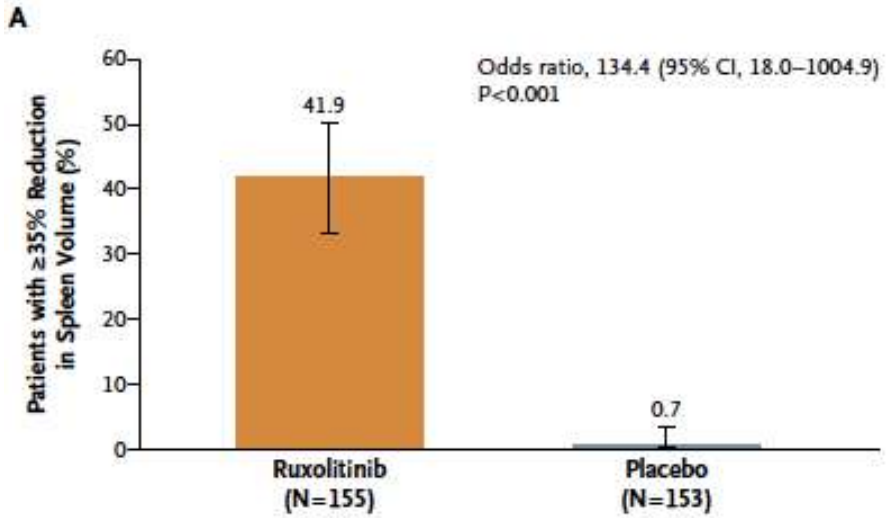
Currently available therapies for MF in the UK

- Hydroxycarbemide
- PEG-Interferon
- Ruxolitinib
  - Intermediate-2 or high risk
- Fedratinib
  - Ruxolitinib failure/intolerance
- Momelotinib
  - GSK EAMS
- Pacritinib
  - Phase 3 randomized trial (vs BAT)
- Erythropoetin analogues
- Red cell transfusion
- Dapsone
- Splenic irradiation

Ruxolitinib in myelofibrosis

COMFORT-1

42% achieved 35% spleen volume reduction at 24 weeks

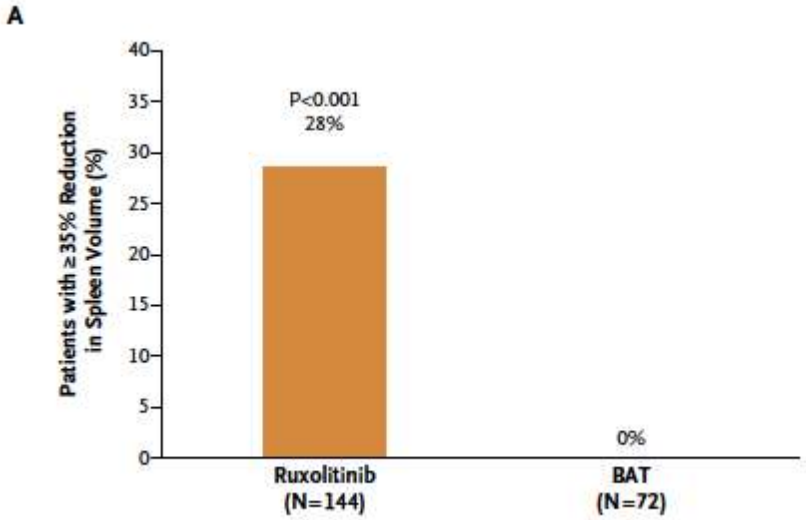


TSS50: 45.9% vs 5.3%

NEJM 2012 366;9: 799

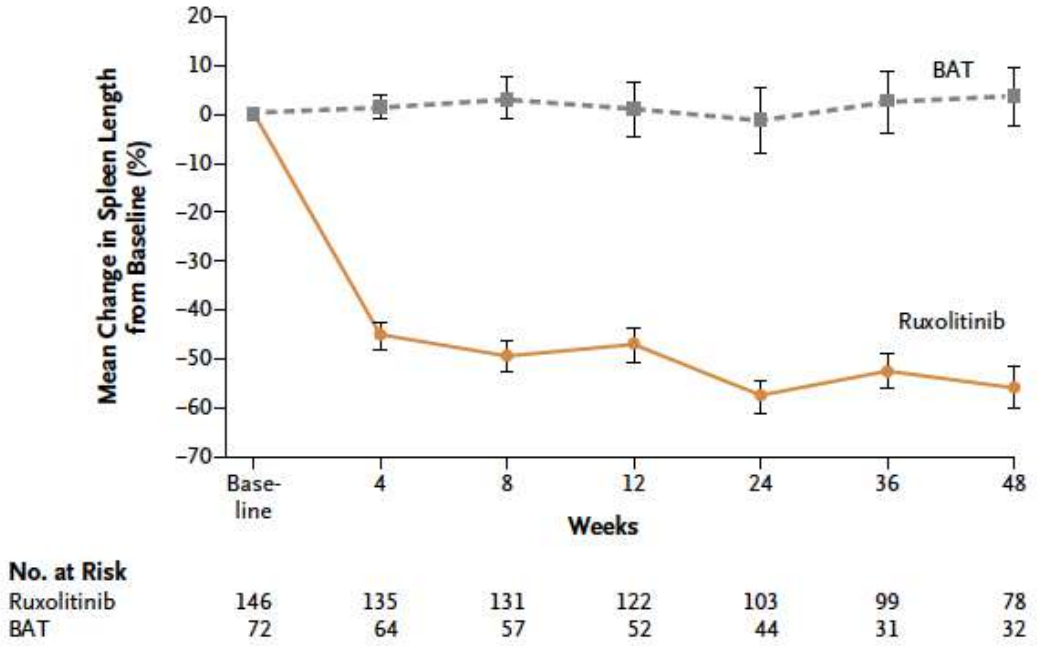
COMFORT-2

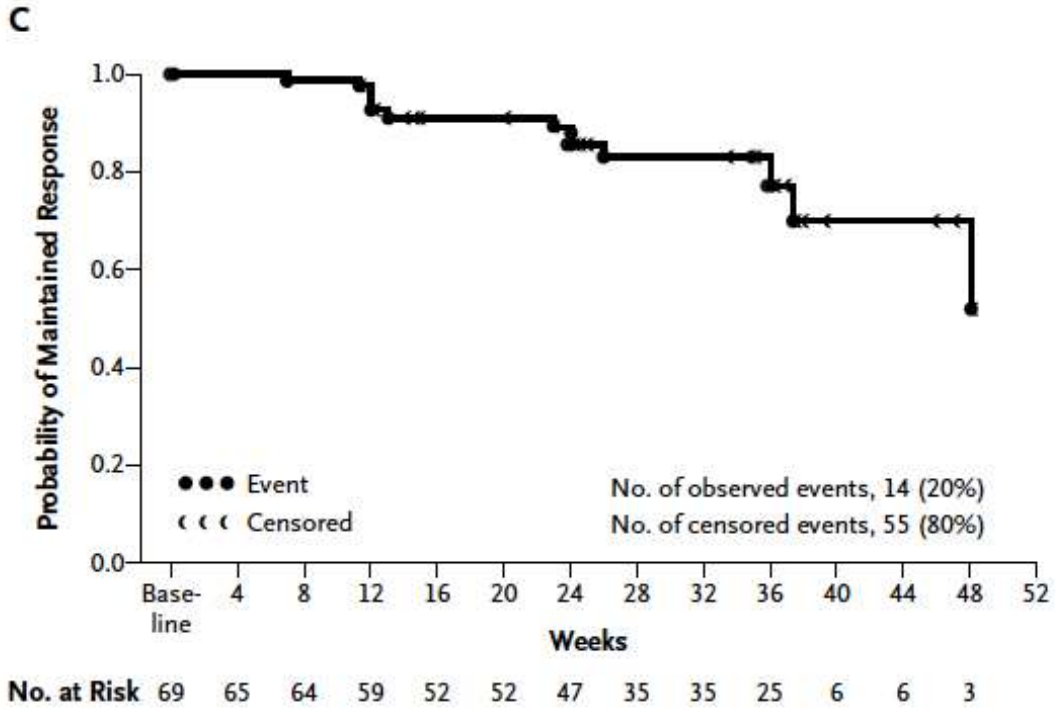
28% achieved 35% spleen volume reduction at 48 weeks



NEJM 2012 366;9: 787

Ruxolitinib in myelofibrosis



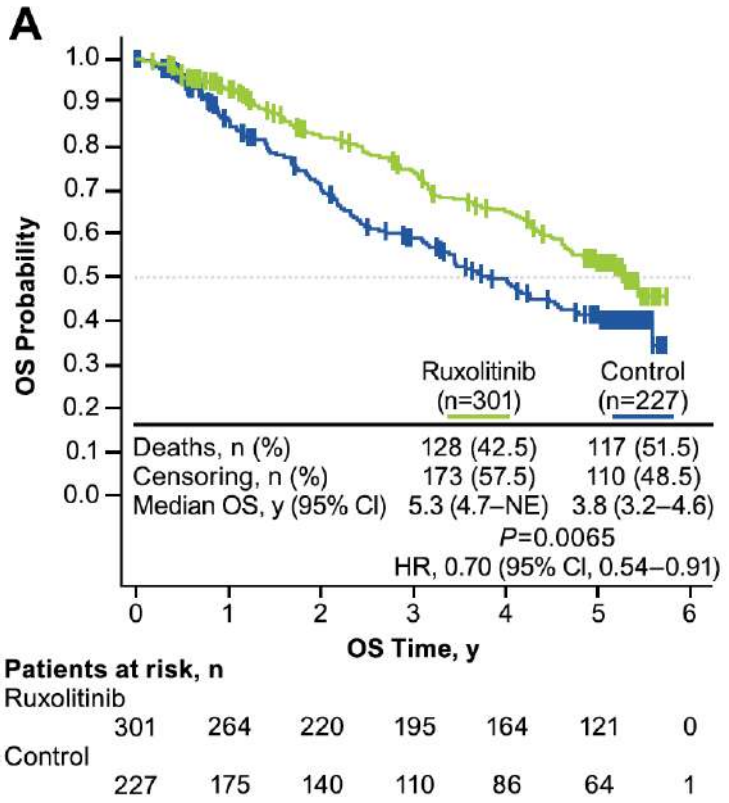


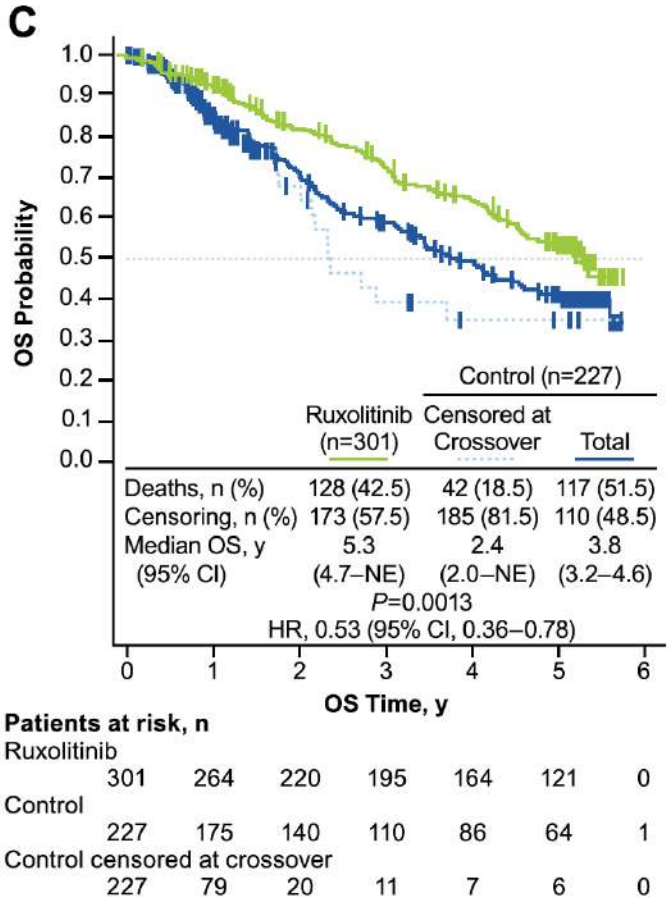
At 83 weeks, 55% remained on rux

Median duration of SVR35 was 3.2 years

NEJM 2012 366;9: 787

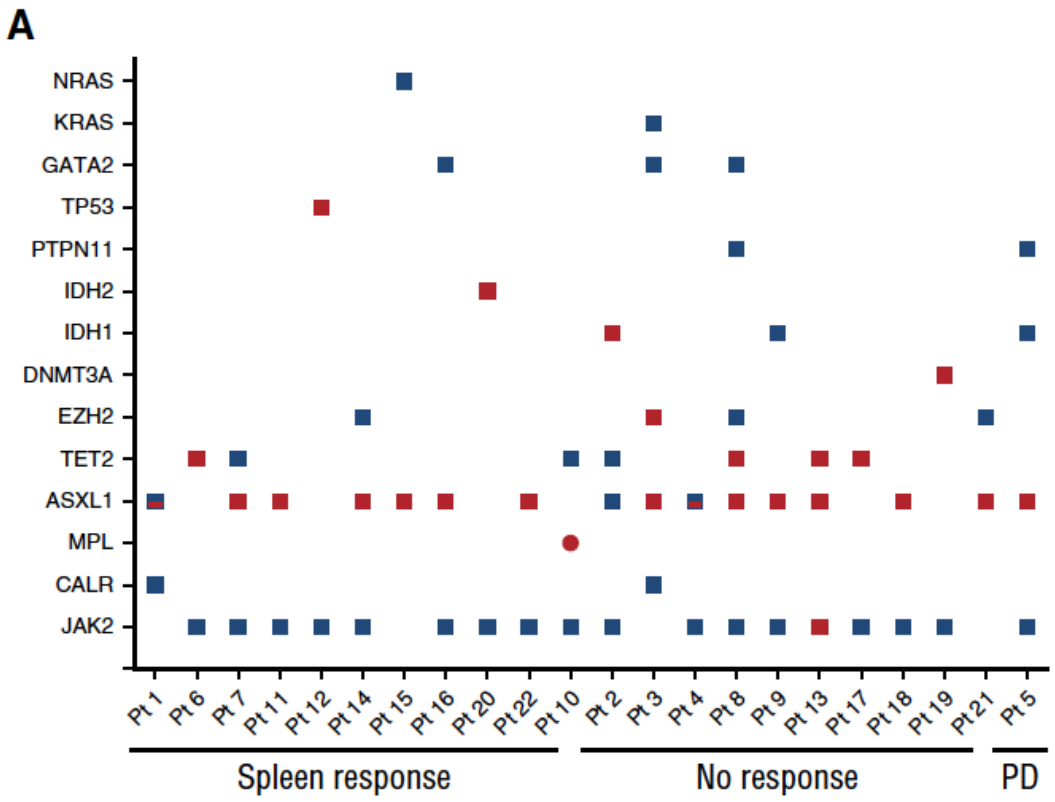
Ruxolitinib in myelofibrosis

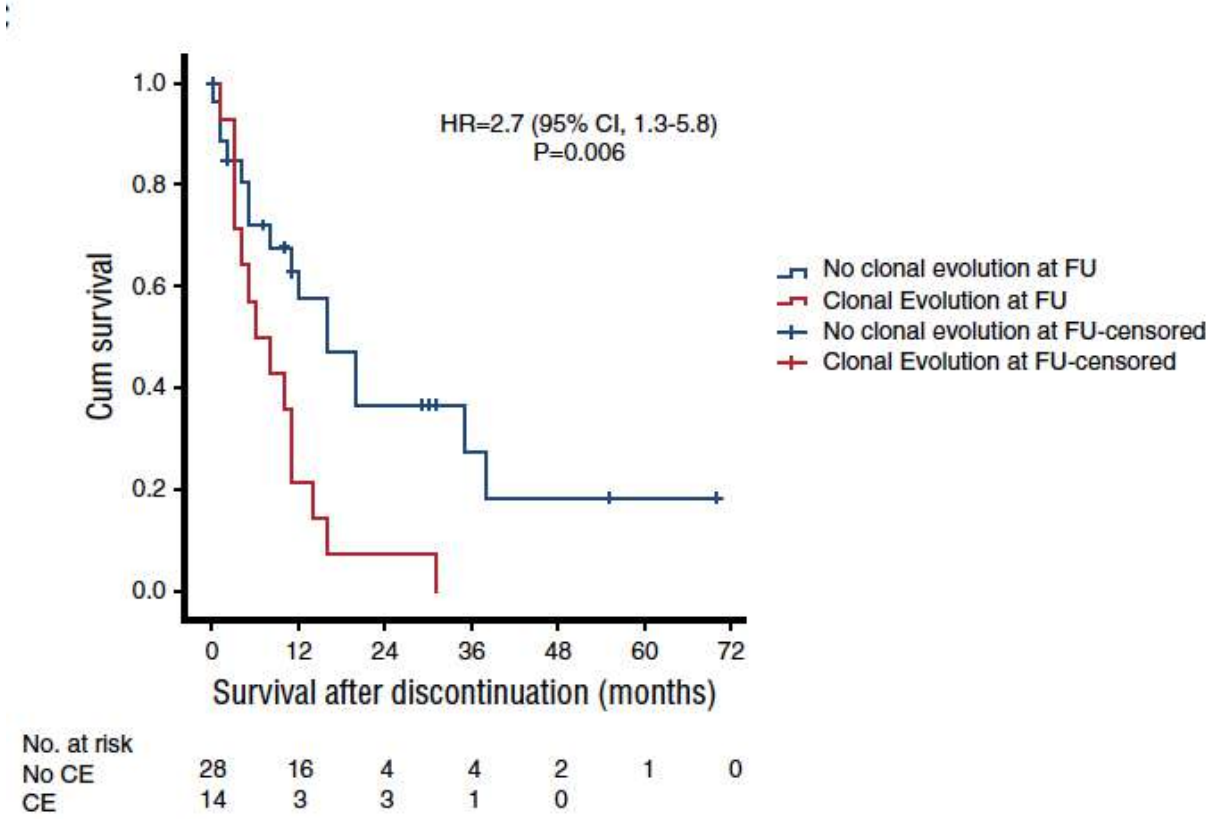




Verstovsek et al. Journal of Hematology & Oncology (2017) 10:156

Clonal Evolution Continues on Ruxolitinib





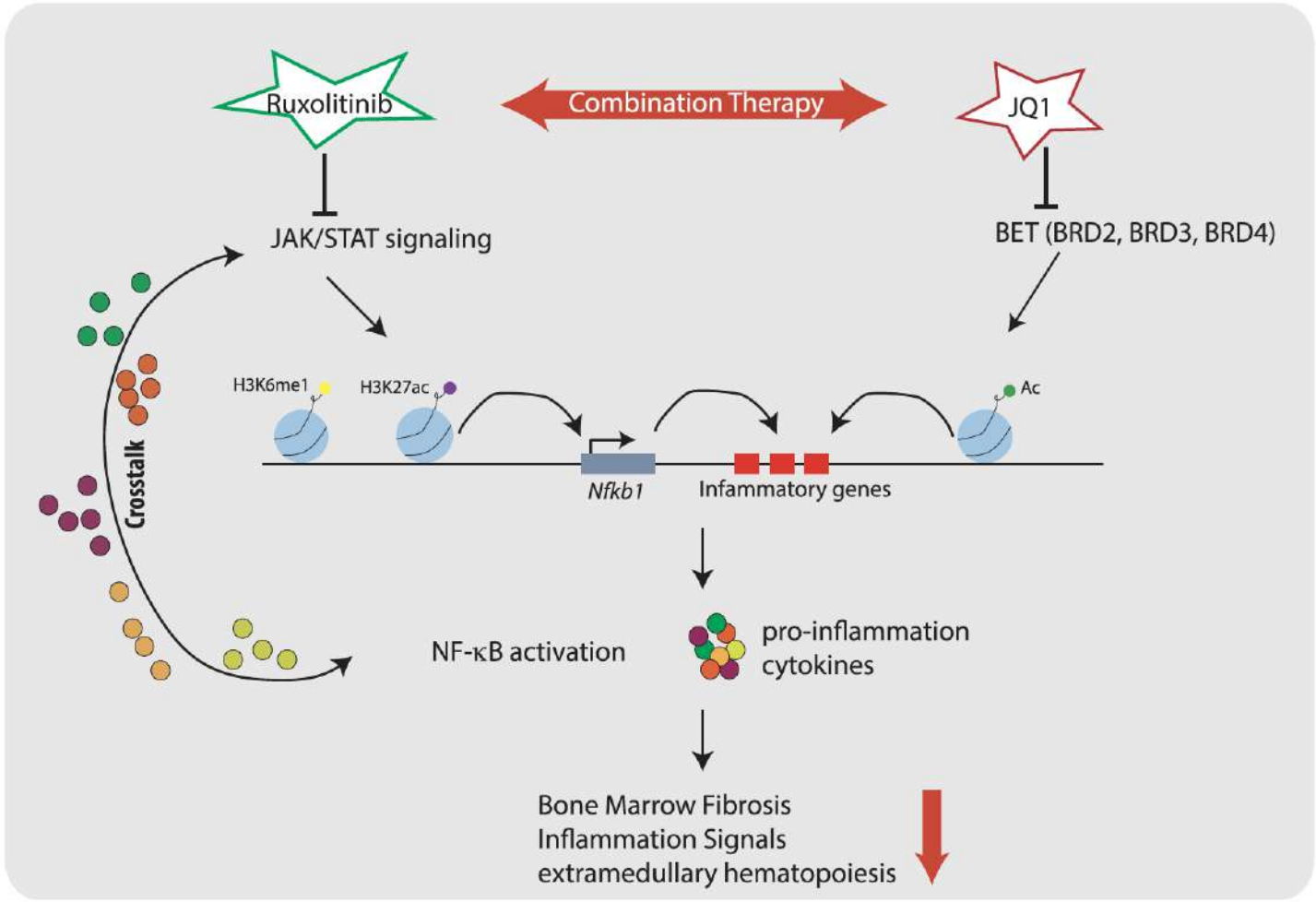
Newburry et al, Blood. 2017;130(9):1125-1131)

Novel Treatment Priorities

- **Better up-front therapies**
  - Alternative JAKi
  - Combination strategies
- **Better mechanism to target the underlying pathology**
  - Molecular responses
  - Immune therapies
- **Better supportive measures**
  - Anaemia

Bromodomain and Extra-Terminal motif (BET) inhibitors

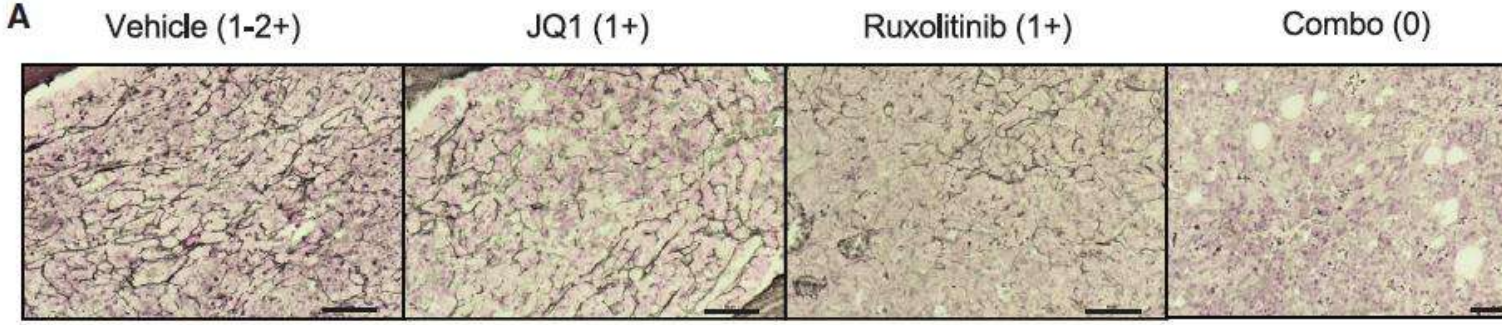
BET inhibitors

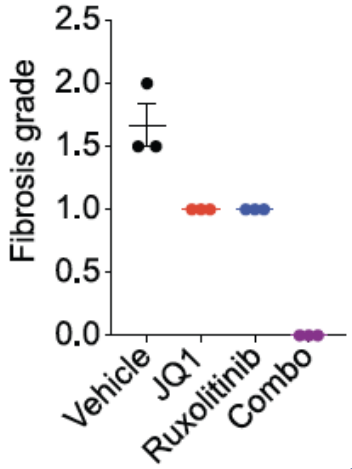


Jiang and Jamieson
Cancer Cell 2018

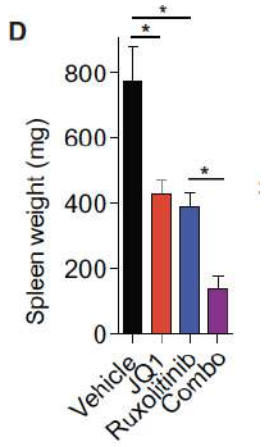
BET inhibitors

Reduction in fibrosis

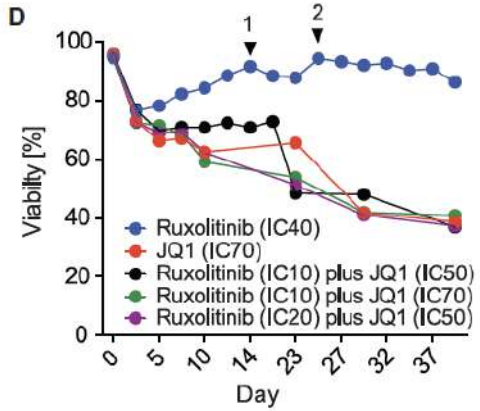


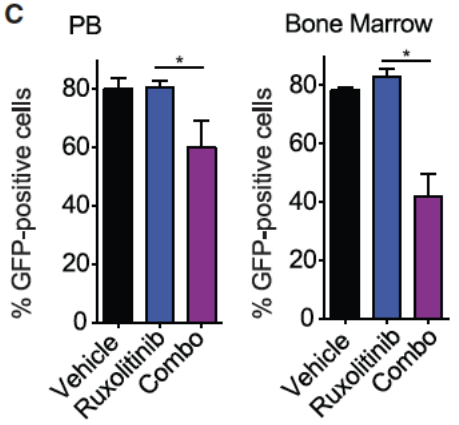


Spleen size reduction



Cell death





Kleppe *et al*
Cancer Cell 2018

Pelabresib in combination with ruxolitinib for Janus kinase inhibitor treatment-naïve patients with myelofibrosis: results of the MANIFEST-2 randomized, double-blind, Phase 3 study

Raajit Rampal,[1] Sebastian Grosicki, Dominik Chraniuk, Elisabetta Abruzzese, Prithviraj Bose, Aaron T Gerds, Alessandro M Vannucchi, Francesca Palandri, Sung-Eun Lee, Vikas Gupta, Alessandro Lucchesi, Stephen Oh, Andrew T Kuykendall, Andrea Patriarca, Alberto Álvarez-Larrán, Ruben Mesa, Jean-Jacques Kiladjian, Moshe Talpaz, Morgan Harris, Sarah-Katharina Kays, Anna Maria Jegg, Qing Li, Barbara Brown, Claire Harrison*, John Mascarenhas*

*Both authors contributed equally

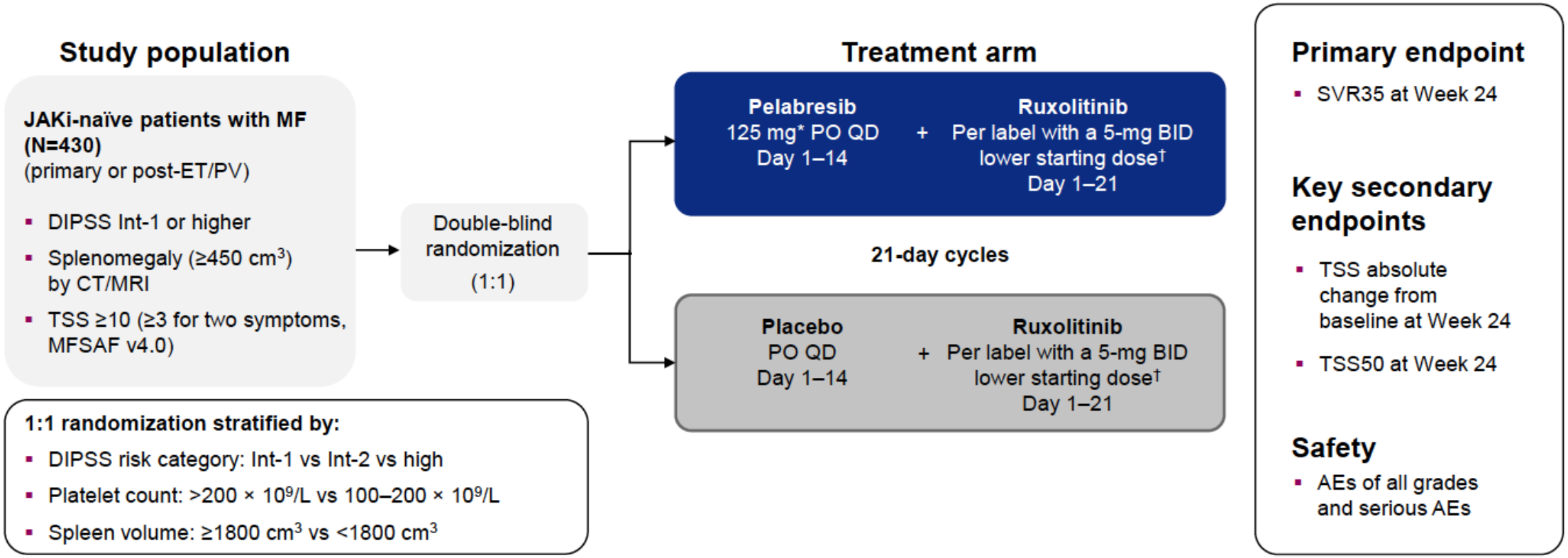
[1]Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Oral 628

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

With permission from Rampal et al

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



AE, adverse event; BID, twice daily; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Int, intermediate; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imagining; PO, orally; PV, polycythemia vera; QD, once daily; SVR35, ≥35% reduction in spleen volume; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score. *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; †Ruxolitinib was started at 10 mg BID (baseline platelet count 100–200 × 10⁹/L) or 15 mg BID (baseline platelet count >200 × 10⁹/L) with a mandatory dose increase by 5 mg BID after one cycle and a maximum dose of 25 mg BID per label. Harrison CN, et al. *Future Oncol*. 2022;18(27):2987-29977.

Rampal R, et al. ASH 2023. Oral 628

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

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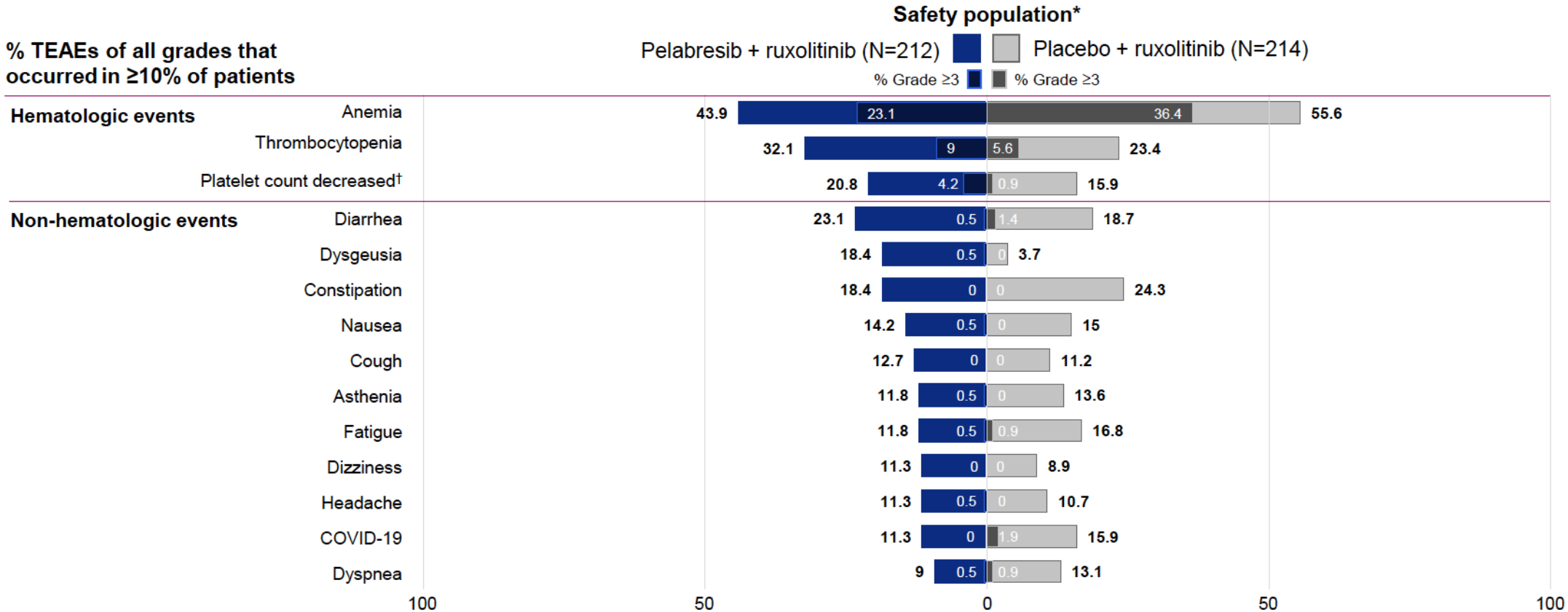
Treatment-emergent adverse events

Adverse events of anemia were reported less frequently with pelabresib + ruxolitinib combination than with placebo + ruxolitinib; no new safety signals were observed



Preliminary Analyses from Data cut off: August 31, 2023. TEAE, treatment-emergent adverse event. *Safety population: received at least one dose of study drug. †Platelet count decreased was classified under the system organ class of investigation. TEAEs are regardless of relationship to study drug. A TEAE for the double-blinded treatment period is defined as an adverse event 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. MF, myelofibrosis; COVID-19, coronavirus disease 2019.

Rampal R, et al. ASH 2023. Oral 628

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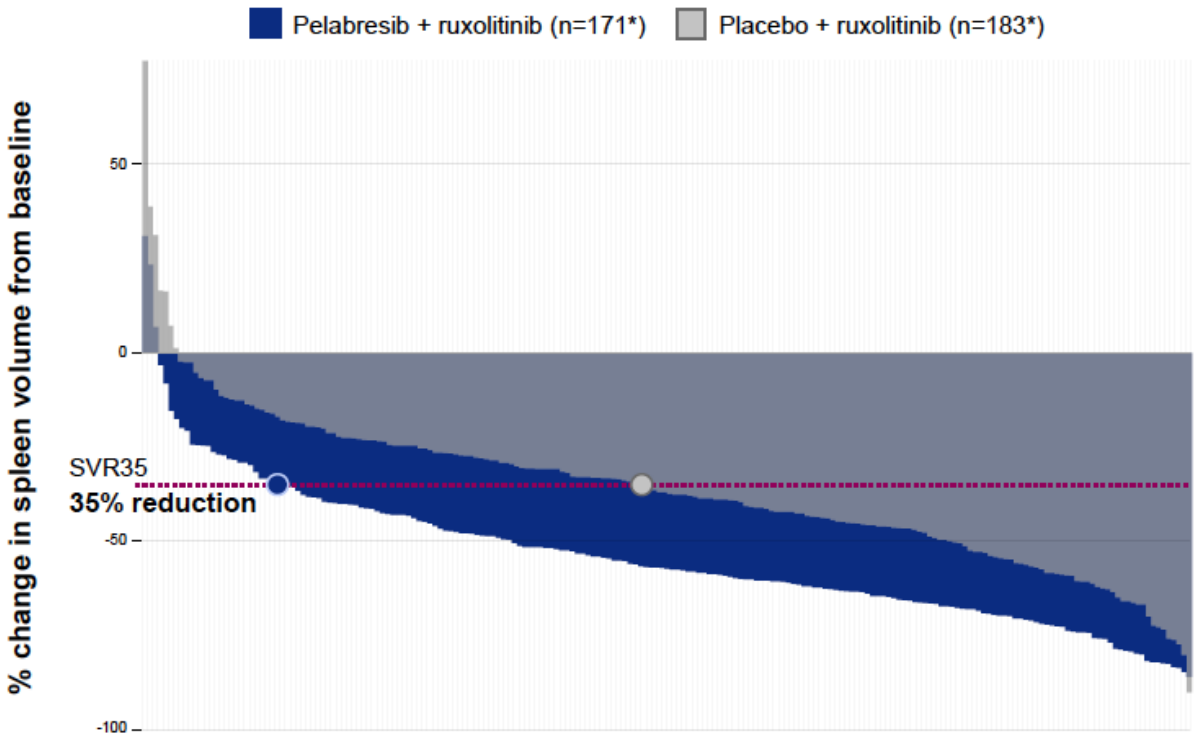
MANIFEST-2 study achieved its primary endpoint: SVR35 at Week 24

Significantly greater response in patients treated with pelabresib + ruxolitinib vs placebo + ruxolitinib



ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	p-value
SVR35 at Week 24	65.9%	35.2%	
Difference† (95% CI)	30.4 (21.6, 39.3)		<0.001
Mean % change in spleen volume at Week 24‡	-50.6 (n=171)	-30.6 (n=183)	
95% CI	-53.2, -48	-33.7, -27.5	

Data cut off: August 31, 2023. CI, confidence interval; ITT, intent-to-treat; SVR35, ≥35% reduction in spleen volume. Spleen volume assessed by central read. *Waterfall plots represent patients who have baseline and Week 24 data. †Calculated by stratified Cochran–Mantel–Haenszel test; ‡Patients without Week 24 assessment are considered non-responders.

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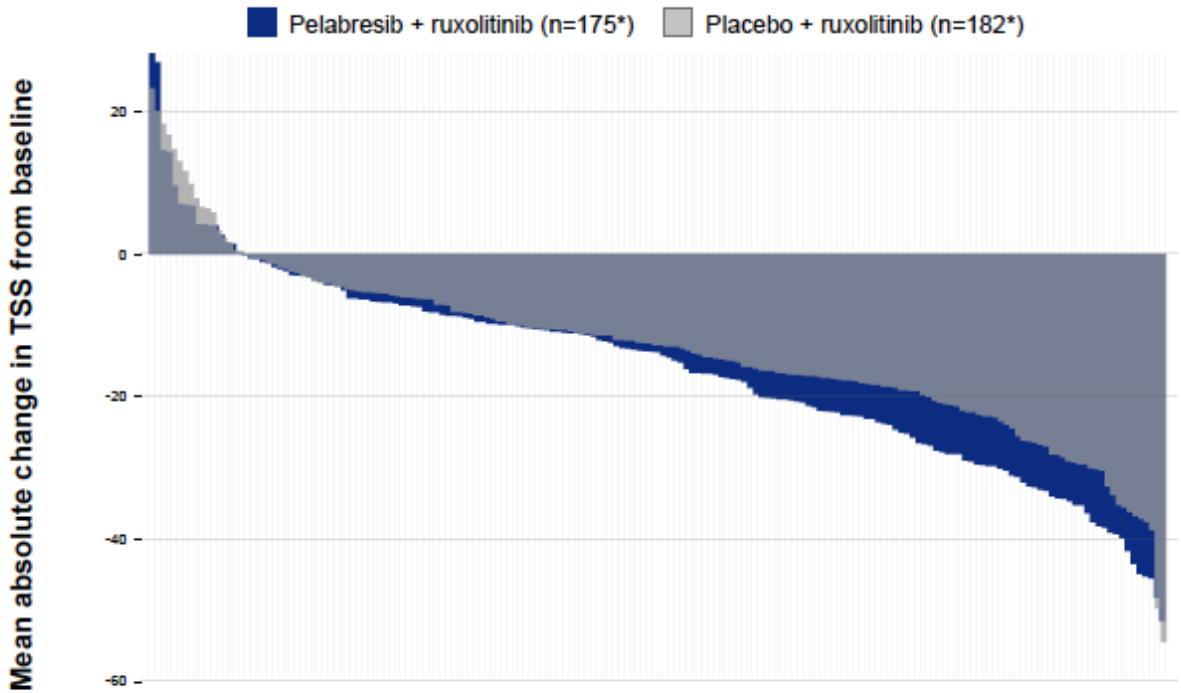
Absolute TSS at Week 24

Strong numerical improvements for patients treated with pelabresib + ruxolitinib vs placebo + ruxolitinib



ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	p-value
TSS change† from baseline at Week 24	-15.99	-14.05	
Mean difference‡ (95% CI)	-1.94 (-3.92, 0.04)		0.0545

- **Absolute change in TSS is a continuous endpoint** that estimates magnitude of symptom burden reduction with enhanced precision

Data cut off: August 31, 2023. ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent-to-treat; TSS, total symptom score. *Waterfall plots represent patients who have baseline and Week 24 data. †Change from baseline determined by ANCOVA model using Multiple Imputation. ‡Least square mean difference from ANCOVA model using baseline DIPSS, baseline platelet count and baseline spleen volume as factors, and baseline TSS as covariate.

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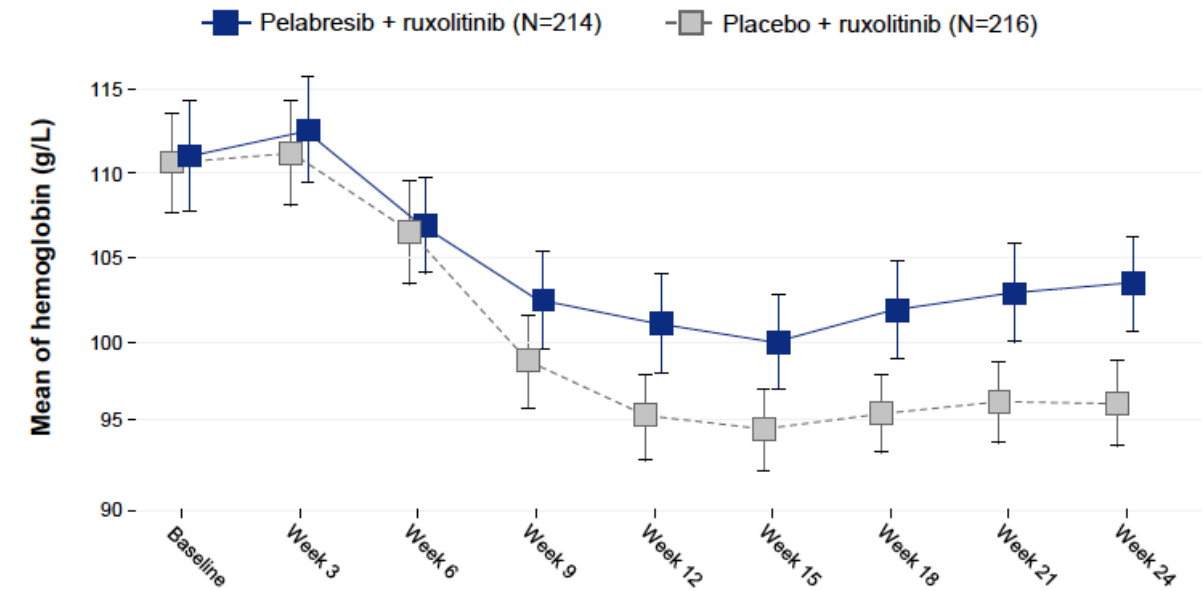
Hemoglobin response

A numerically greater proportion of patients achieved hemoglobin response with pelabresib + ruxolitinib vs placebo + ruxolitinib



Number of patients

Pelabresib + ruxolitinib	212	204	209	199	193	189	186	185	184
Placebo + ruxolitinib	214	206	211	209	207	205	204	199	196

ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
Hemoglobin response* ≥1.5 g/dL mean increase (95% CI)	9.3% (5.45, 13.25)	5.6% (2.50, 8.61)
Patients requiring RBC transfusion during screening, n (%)	35 (16.4)	25 (11.6)
Patients requiring RBC transfusion during first 24 weeks of study treatment, n (%)	66 (30.8)	89 (41.2)

Preliminary Analyses from Data cut off: August 31, 2023. CI, confidence interval; RBC, red blood cell. *Hemoglobin response is defined as a ≥1.5 g/dL mean increase in hemoglobin from baseline in the absence of transfusions during the previous 12 weeks. Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. A similar effect was observed across DIPSS categories.

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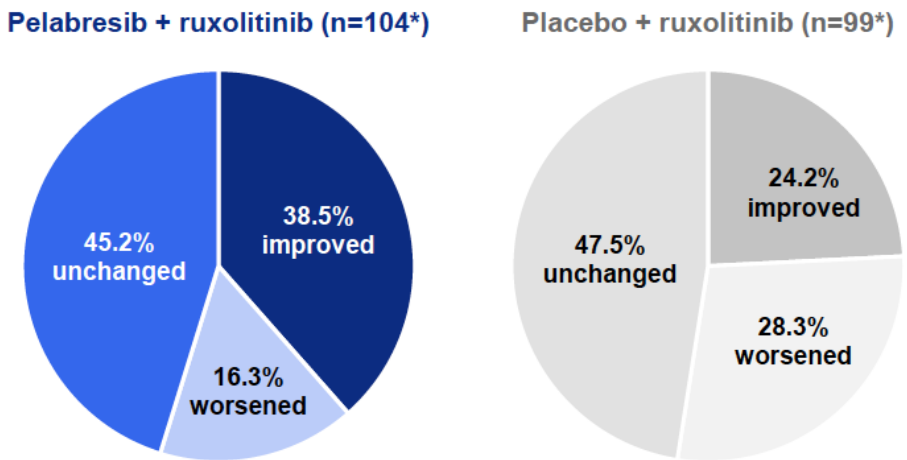
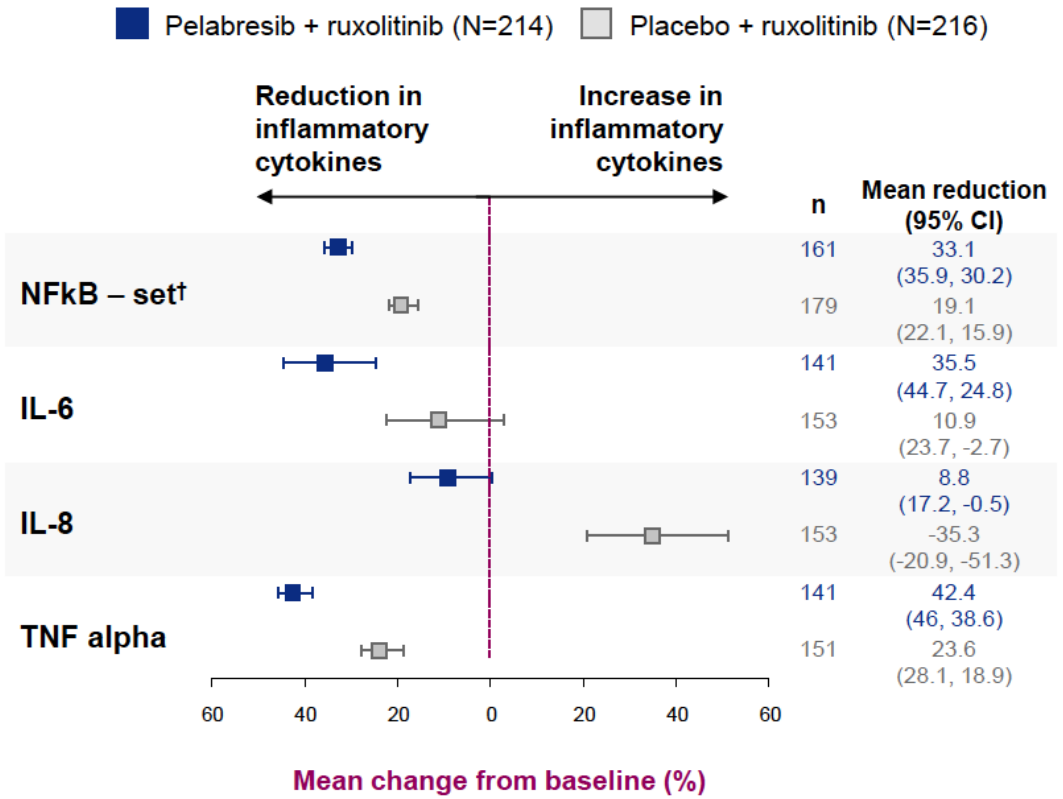
Reduction in bone marrow fibrosis and inflammatory cytokines

Improvement of reticulin fibrosis grade in central read by Week 24



	Pelabresib + ruxolitinib	Placebo + ruxolitinib	Odds ratio
Worsened ≥1 grade (%)	16.3	28.3	0.47 (0.23-0.92)
Improved ≥1 grade (%)	38.5	24.2	2.09 (1.14-3.93)

Reduction of inflammatory cytokines by Week 24



Preliminary Analyses from Data cut off: August 31, 2023. IL-6, interleukin 6; IL-8, interleukin 8; NFκB, Nuclear factor kappa-light-chain-enhancer of activated B cells; TNF, tumor necrosis factor. *n=203 evaluable patients (baseline & C9D1). †NFκB - set includes: B2M, CRP, CD40-L, HEPCIDIN, IL-6, IL-12p40, MIP-1 BETA, MPIF-1, RANTES, TNFR2, TNF alpha, VCAM-1.

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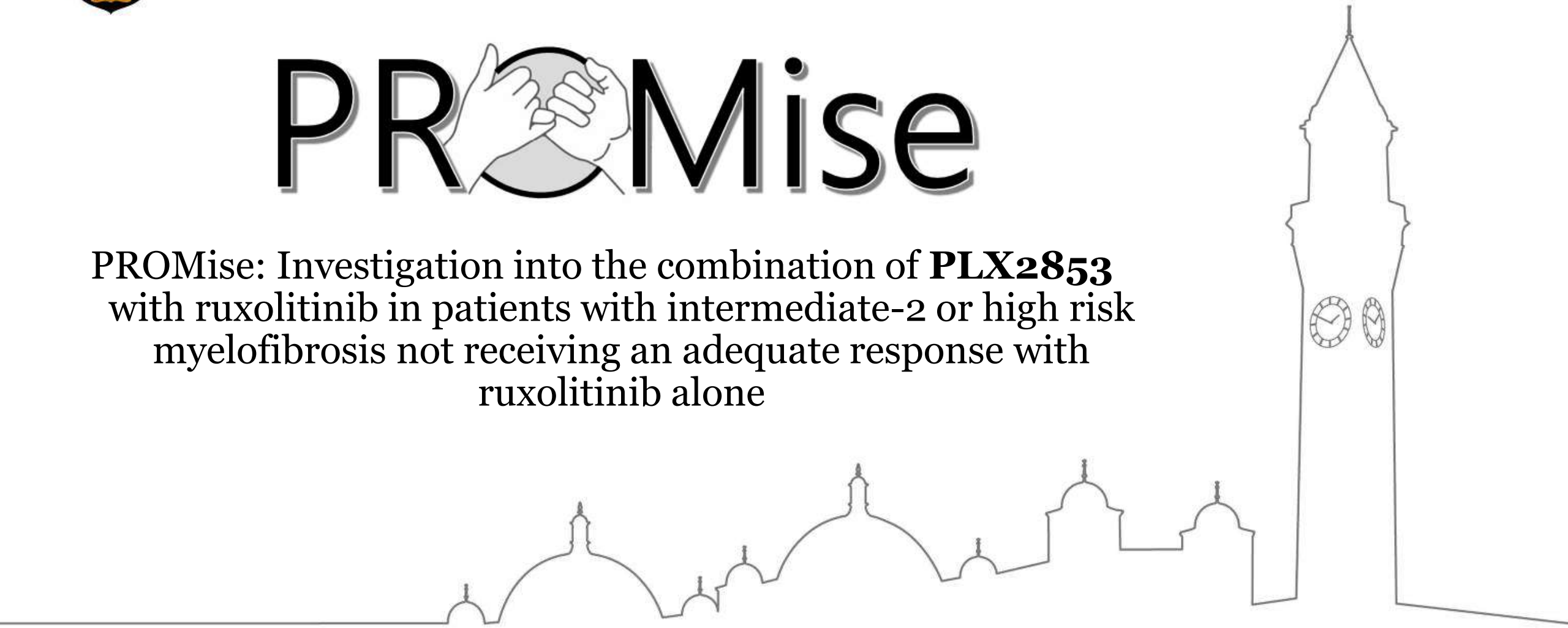
PROMise

PROMise: Investigation into the combination of **PLX2853** with ruxolitinib in patients with intermediate-2 or high risk myelofibrosis not receiving an adequate response with ruxolitinib alone



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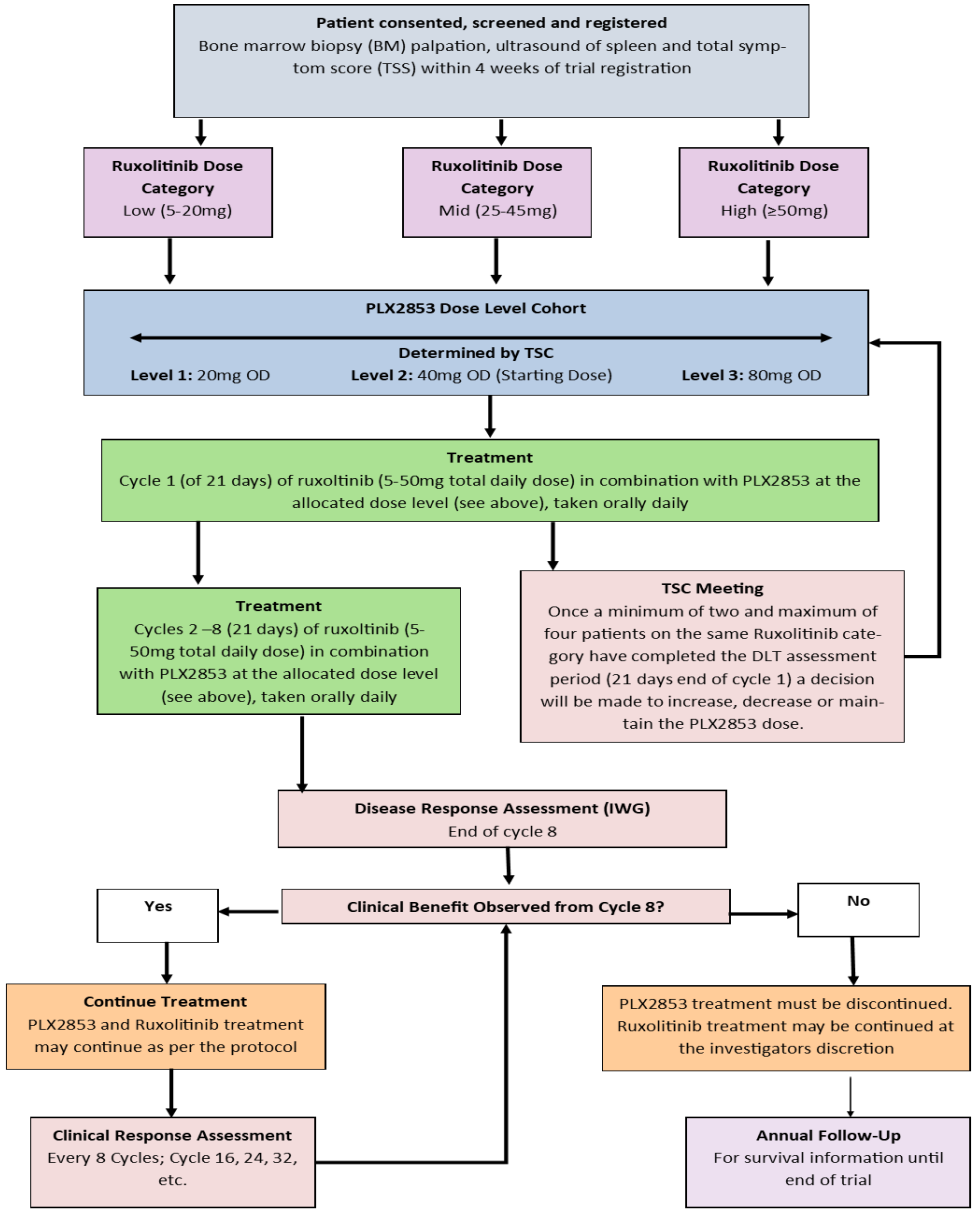
PROMise

- Patients with Primary or Secondary Myelofibrosis who have been treated with Ruxolitinib for over 24 weeks
- Patients have ongoing residual splenomegaly, and are not receiving an adequate response with Ruxolitinib alone
- PROMise is a dose finding trial assessing PLX2853 (BET Inhibitor) in conjunction with Ruxolitinib



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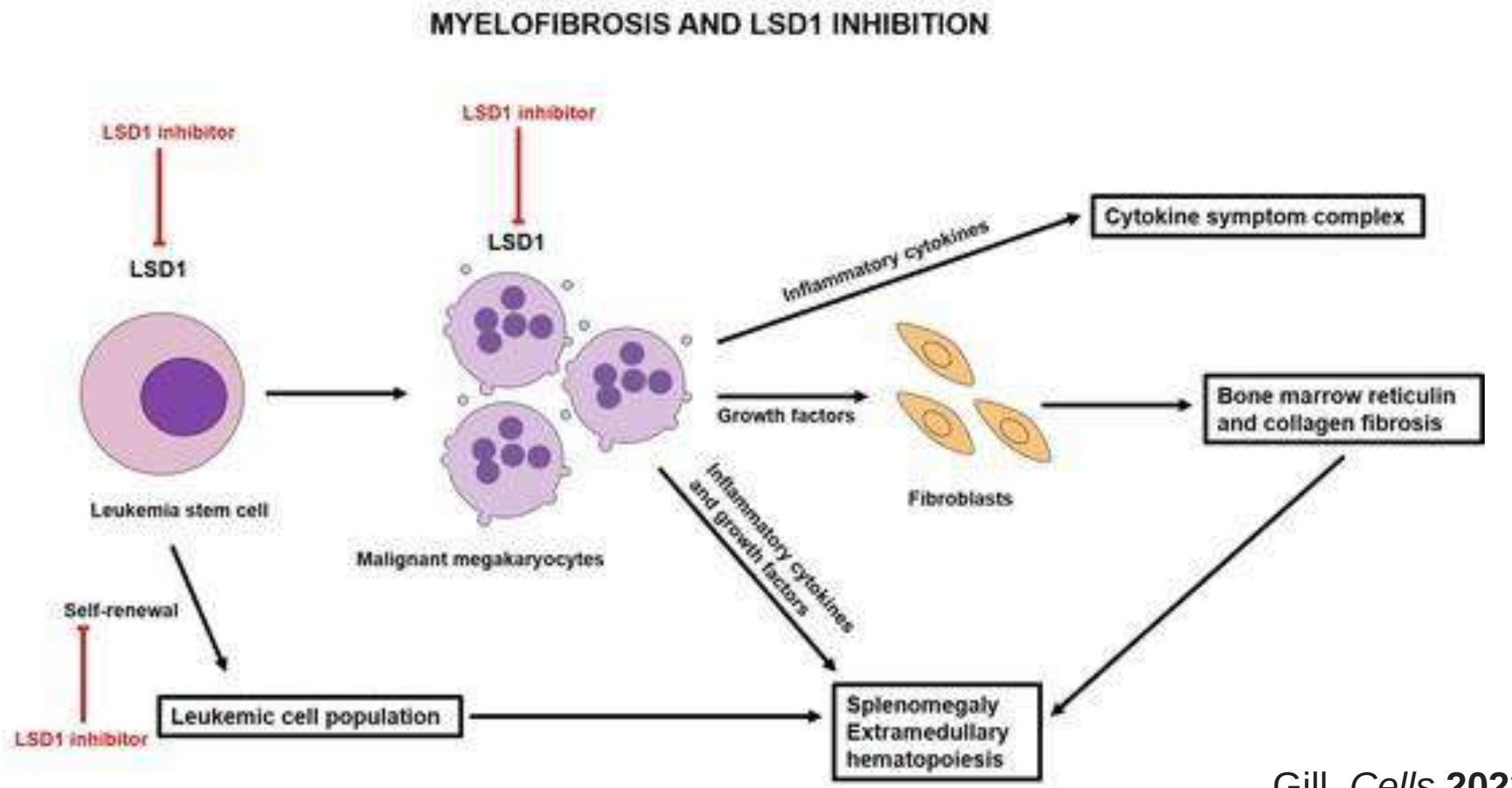
Lysine specific demethylase-1 (LSD1) inhibitors

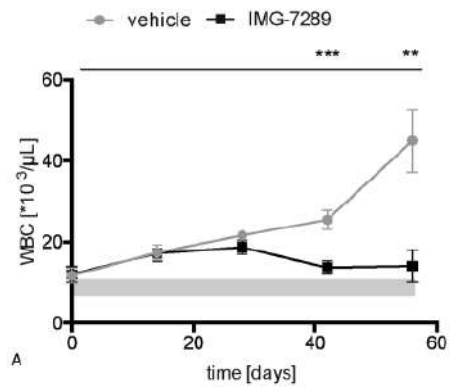
Bomedemstat

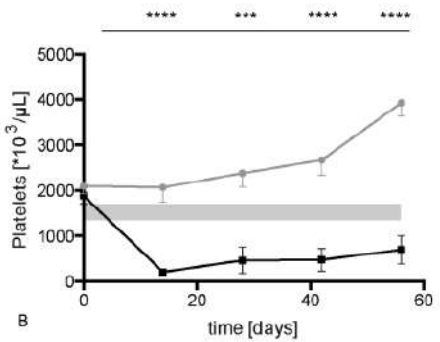
LSD-1 Inhibitors

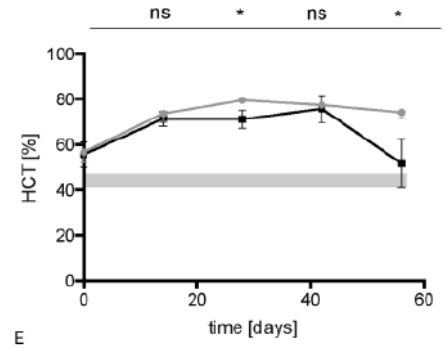


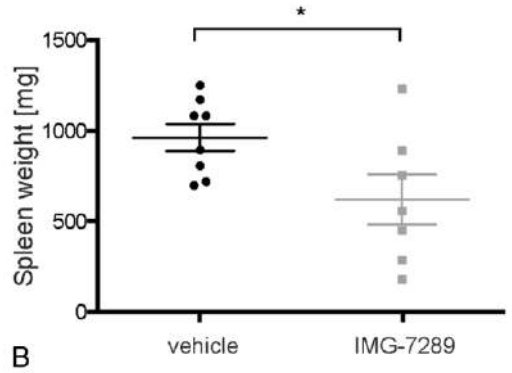
Gill, *Cells* **2022**, *11*(13)

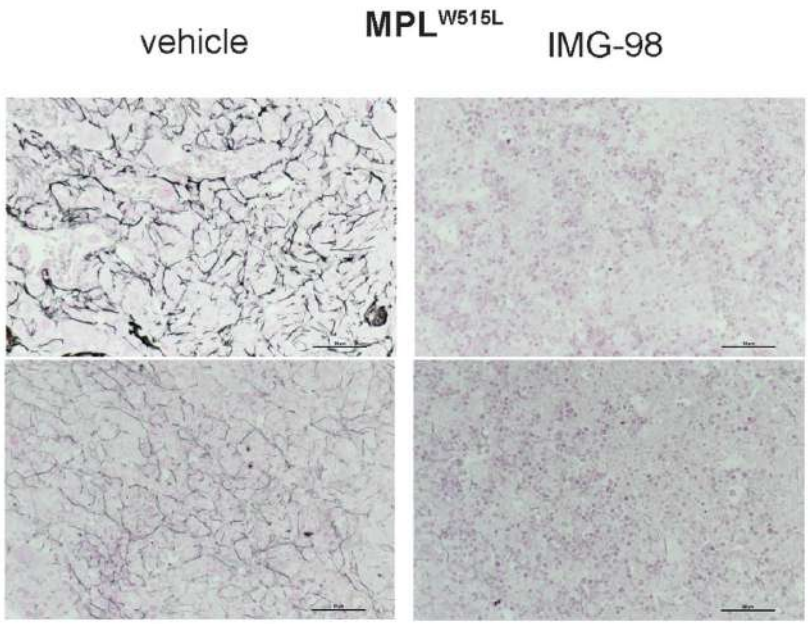
LSD1 Inhibition Prolongs Survival in Mouse Models of MPN by Selectively Targeting the Disease Clone



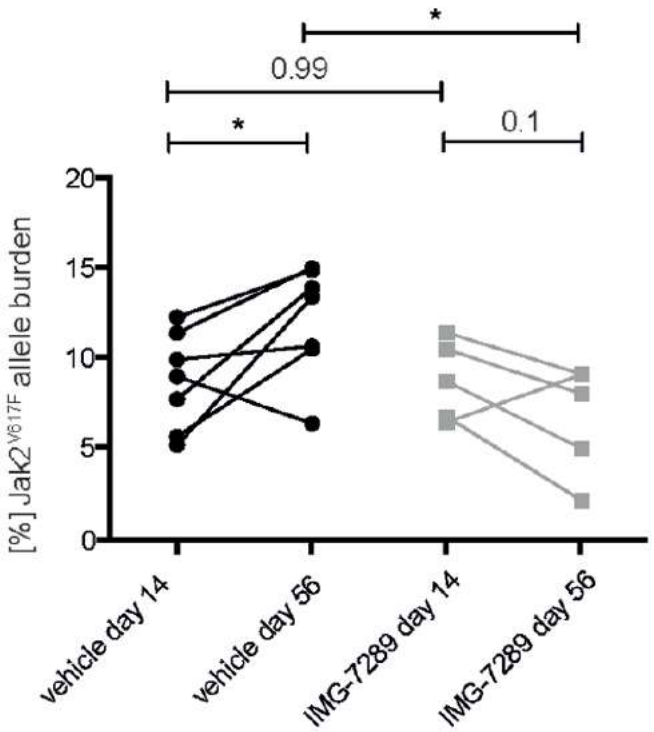








Jak2 clone size



Jutzi et al HemaSphere, 2018;2:3

Bomedemstat, an LSD1 Inhibitor, Manages the Signs and Symptoms of Essential Thrombocythemia While Reducing the Burden of Cells Homozygous for Driver Mutations

Joachim R. Göthert[1]; Harinder Gill[2]; Francesca Palandri[3]; David M. Ross[4]; Tara Cochrane[5]; Stephen R. Larsen[6]; Anna B. Halpern[7]; Jake Shortt[8]; James M. Rossetti[9]; James Liang[10]; Monia Marchetti[11]; Andrew J. Wilson[12]; Andrew Innes[13]; Merit Hanna[14]; William S. Stevenson[15]; Alessandro Vannucchi[16]; Maria Kleppe[17]; Georges Natsoulis[17]; Claire N. Harrison[18]; Hugh Young Rienhoff, Jr.[17]

[1]Department of Hematology and Stem Cell Transplantation, West German Cancer Center (WTZ), University Hospital Essen, Essen, Germany; [2]Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong, China; [3]Institute of Hematology "L. & A. Seràgnoli," Sant'Orsola-Malpighi University Hospital, Bologna, Italy; [4]Department of Haematology, Royal Adelaide Hospital and SA Pathology, Adelaide, SA, Australia; [5]Department of Haematology, Gold Coast University Hospital, Southport, QLD, Australia; [6]Institute of Haematology, Royal Prince Alfred Hospital, Sydney, NSW, Australia; [7]Division of Hematology and Oncology, University of Washington, and Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA, USA; [8]Monash Haematology, Monash Health, Clayton, VIC, Australia; [9]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [10]Middlemore Clinical Trials, Auckland, New Zealand; [11]Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [12]University College London Hospitals NHS Foundation Trust, London, United Kingdom; [13]Imperial College Healthcare NHS, London, United Kingdom; [14]North Shore Hospital, Waitemata District Health Board, Auckland, New Zealand; [15]Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney, NSW, Australia; [16]University of Florence, AOU Careggi, CRIMM, Center for Research and Innovation of Myeloproliferative Neoplasms, Florence, Italy; [17]Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; [18]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

With permission from Gothert et al

Study Design (NCT04254978)

Key Eligibility Criteria

- Age ≥18 years
- Diagnosis of ET per WHO diagnostic criteria[1]
- Required cytoreduction based on age (>60 years) or history of thrombosis
- Inadequate response or intolerant to ≥1 standard therapy
- Platelet count >450 × 10^9/L
- Hemoglobin ≥100 g/L
- ECOG performance status 0-2
- No prior splenectomy

Initial 24-Week Treatment Period

Bomedemstat
Starting dose: 0.6 mg/kg/day PO

Titrated to a target platelet count of 200-400 × 10^9/L

Additional 24-Week Treatment Periods[a]

Bomedemstat
0.6 mg/kg/day PO

Titrated to a target platelet count of 200-400 × 10^9/L

Primary End Points

- Safety and tolerability
- Response, defined as platelet count ≤400 × 10^9/L without new thromboembolic events

Exploratory End Points

- Hematologic effects
- Durable reduction in platelets (≤400 × 10^9/L for ≥12 weeks)
- Durable reduction in WBCs (<10 × 10^9/L for ≥12 weeks)
- Patient reported symptom burden (MPN-SAF and PGIC)
- Thrombotic and hemorrhagic events
- Mutant allele burden[b]
- Transformation to AML

[a]Patient responses were reviewed every 24 weeks and those considered by the investigator to be deriving clinical benefit could remain on study. [b]Assessed by deep sequencing (median exonic depth of 1784 reads) of 261 genes of germline and somatic DNA. Homozygosity of mutant alleles was imputed when variant allele frequency was >50% and/or loss of heterozygosity was detected based on the difference between the minor allele frequency of flanking single nucleotide polymorphisms in germline versus granulocyte DNA. Single cell genotypes were determined in stem/progenitor (CD34+) and monocyte (CD14+) cells in patients with loss of heterozygosity using the Tapestri® system.

1. Arber DA et al. *Blood*. 2016;127:2391-2405.

With permission from Gothert et al

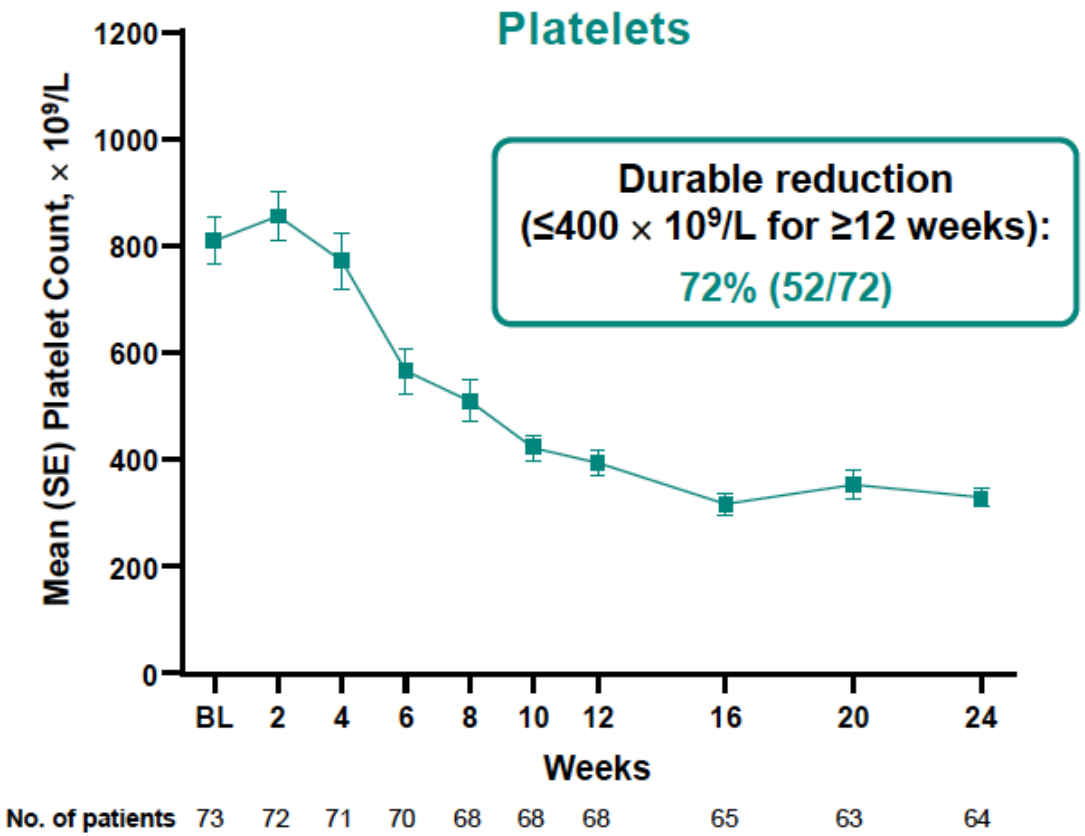
Safety

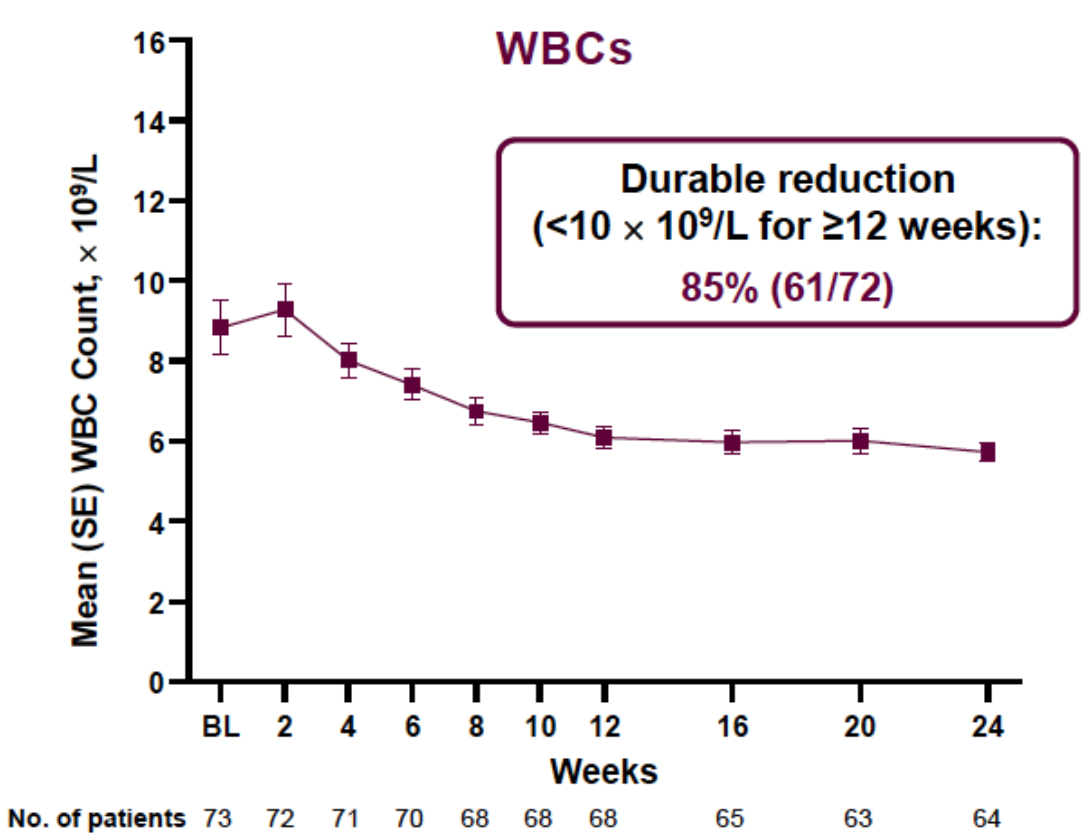
- In the overall treatment period, bomedemstat was administered for a median of 336 days (range, 1-832)
- Median daily dose in the overall treatment period: 0.75 mg/kg/day (range, 0.3-1.4)
- 1 patient experienced transformation to acute myeloid leukemia between weeks 24 and 48[a]

n (%)	Bomedemstat N = 73	
Any AE	73 (100)	
Grade 3/4 AEs	34 (47)	
Serious AEs	27 (37)	
AEs that led to temporary interruption of treatment	29 (40)	
AEs that led to permanent discontinuation of treatment	11 (15)	
Died because of AEs	0 (0)	
AEs in ≥20% of patients	**Any grade**	**Grade 3/4**
Dysgeusia	42 (58)	0 (0)
Arthralgia	29 (40)	4 (5)
Constipation	29 (40)	1 (1)
Thrombocytopenia	26 (36)	10 (14)
COVID-19	20 (27)	0 (0)
Fatigue	20 (27)	0 (0)
Contusion	19 (26)	2 (3)
Diarrhea	15 (21)	1 (1)

With permission from Gothert et al

Effect on Platelets and White Blood Cells



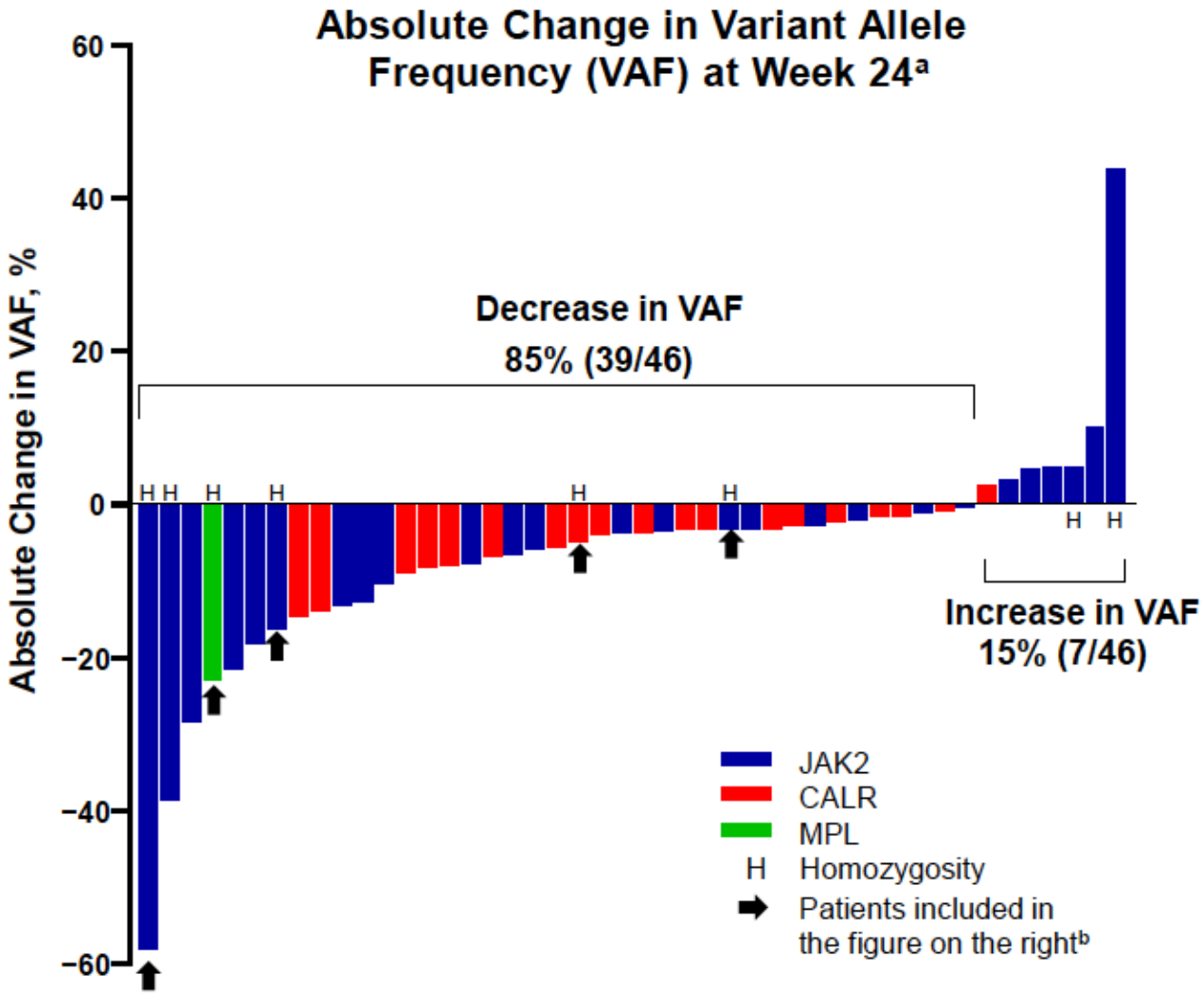


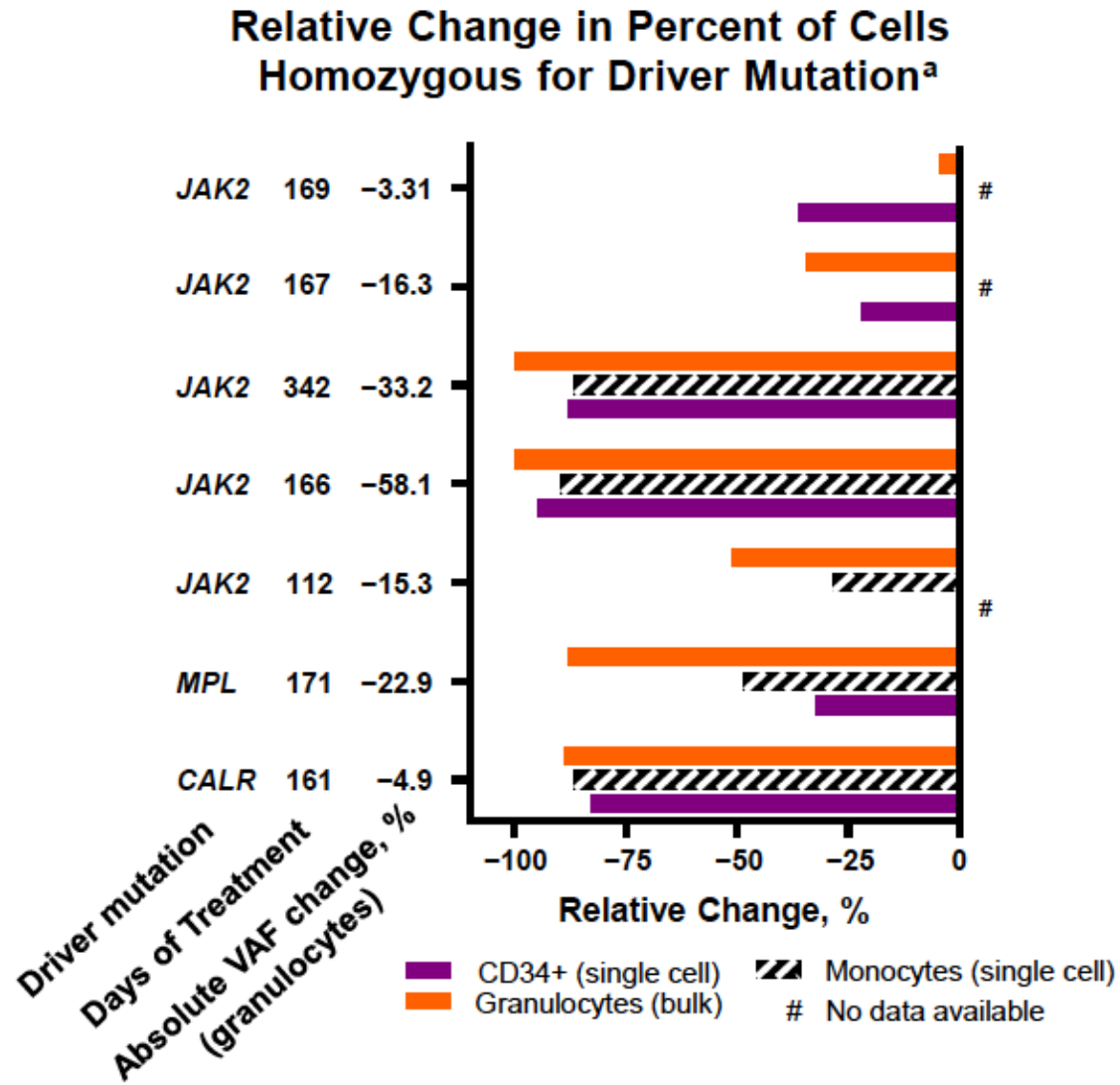
- Hemoglobin levels remained stable throughout the initial 24-week treatment period

Data cutoff date: May 03, 2023.

With permission from Gothert et al

Changes in Mutant Allele Burden





[a]10 patients were homozygous for driver clones, but 2 are not shown on the figure because they had discontinued treatment before week 24. [b]2 patients in the figure on the right did not have data available at week 24. Data cutoff date: May 03, 2023.

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

Inclusion
- IPSS int. or high-risk patients
- Refractory, resistant, poorly controlled, or intolerant to JAK inhibition
- Platelet count ≥100 x 10^9/L

N=89

82% prior ruxolitinib

70% had also received ≥1 other treatments

IPSS: High 53%, Int-2 40%, Int-1 7%

JAK2 (65%), *CALR* (22%),
or *MPL* (7%)
61% had ≥2 mutations of which 67% had ≥1 high-molecular risk mutation (*e.g.*, *ASXL1, IDH1/2, EZH2, SRSF2*)

SVR
- 66% had a reduction from baseline
- 28% ≥20% SVR
- 6% showing ≥35% SVR

TSS ≥20
- 65% reported a reduction
- 19% reported ≥ 50% reduction

14% became transfusion independent

85% improved by ≥1 grade or were stable
- 53% with improved fibrosis saw increased Hb

42% showed a reduction in VAF

Blood (2022) 140 (Supplement 1): 9717–9720.

Nuclear-cytoplasmic transport inhibitors – XPO1

Selinexor

Nuclear–Cytoplasmic Transport Is a Therapeutic Target in Myelofibrosis

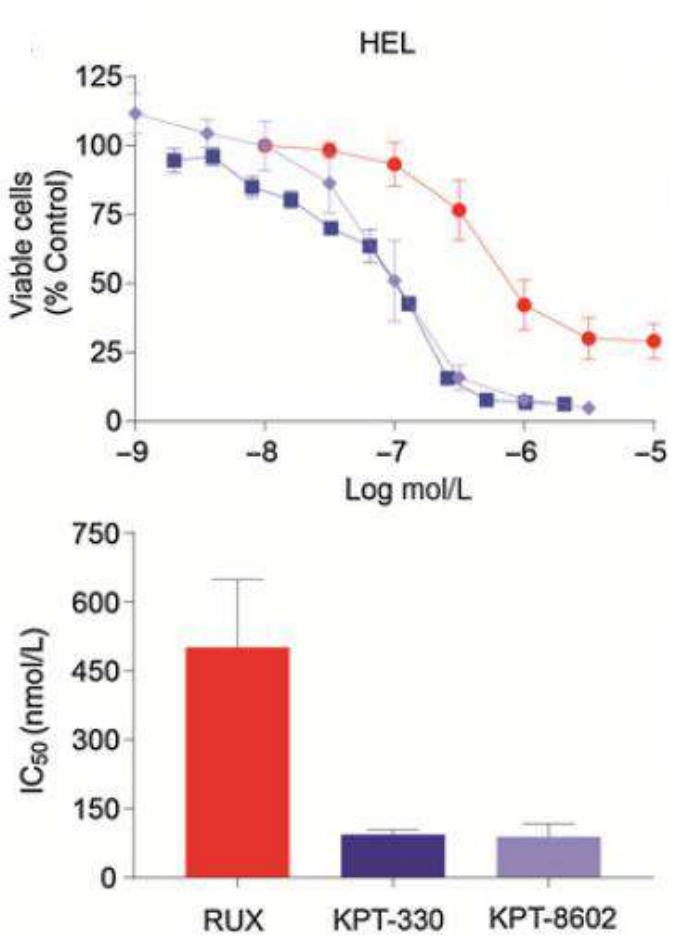
Table 1. The top 20 hits from the shRNA library screen

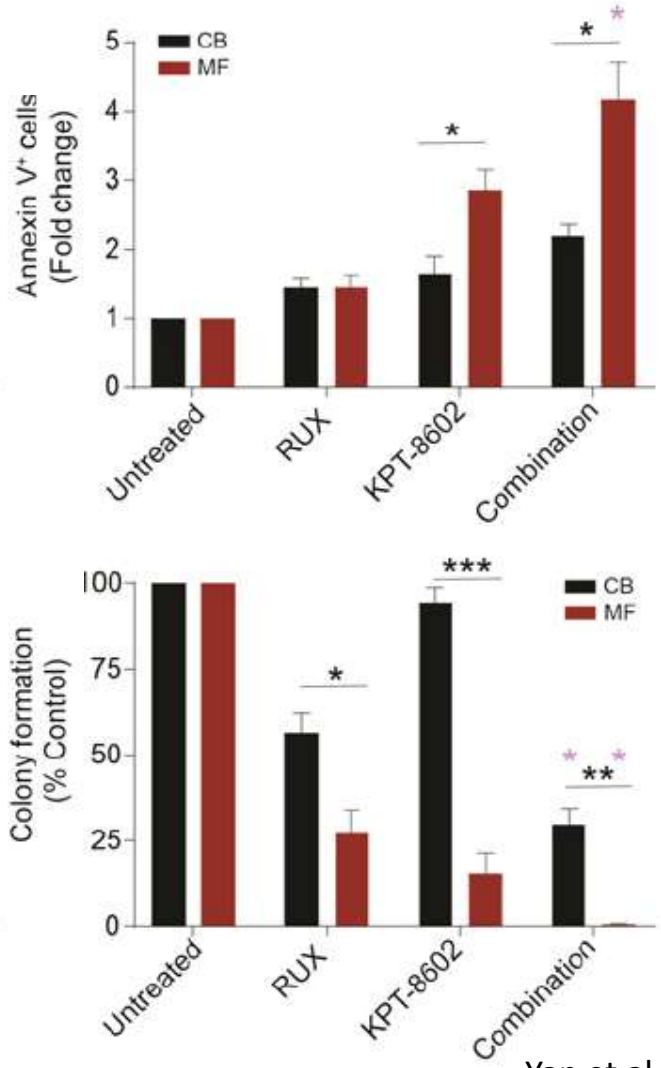
Rank	Gene symbol	Median fold depletion	Gene name	Group
1	PSMB2	59	Proteasome subunit beta 2	P
2	RAN	50	RAN family GTPase, Ras superfamily GTPase	N
3	SHFM1	45	26S proteasome complex subunit	P
4	IL28B	43	Interferon lambda 3	O
5	PSMD13	41	Proteasome 26S subunit, non-ATPase 13	P
6	POLR2F	40	RNA polymerase II subunit F	T
7	RPL11	40	Ribosomal protein L11	T
8	PSMD2	38	Proteasome 26S subunit, non-ATPase 2	P
9	SSRP1	36	Structure specific recognition protein 1	T
10	RPL12	36	Ribosomal protein L12	T
11	HMGCR	35	3-hydroxy-3-methylglutaryl-CoA reductase	M
12	RPL6	34	Ribosomal protein L6	T
13	HNRNPC	34	Heterogeneous nuclear ribonucleoprotein C (C1/C2)	T
14	ITK	33	IL2 inducible T-cell kinase	O
15	SIN3A	33	SIN3 transcription regulator family member A	T
16	RANBP2	33	RAN binding protein 2	N
17	PSMA3	33	Proteasome subunit alpha 3	P
18	PSMB7	33	Proteasome subunit beta 7	P
19	LOC402057	32	Unknown gene, NM_001080499.1	O
20	PSMB3	32	Proteasome subunit beta 3	P

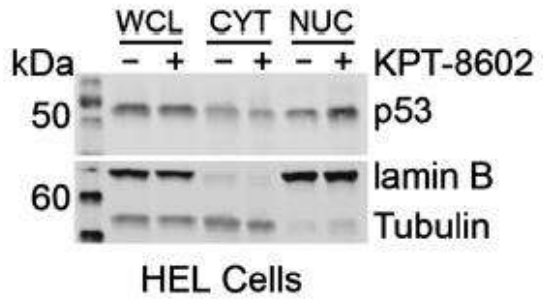
Abbreviation: M, metabolism (1); N, nuclear–cytoplasmic transport (2); O, other (3); P, proteasome (7); T, transcription, translation (7).

Yan et al Clin Cancer Res. 2019 Apr 1;25(7):2323-2335

Nuclear–Cytoplasmic Transport Is a Therapeutic Target in Myelofibrosis

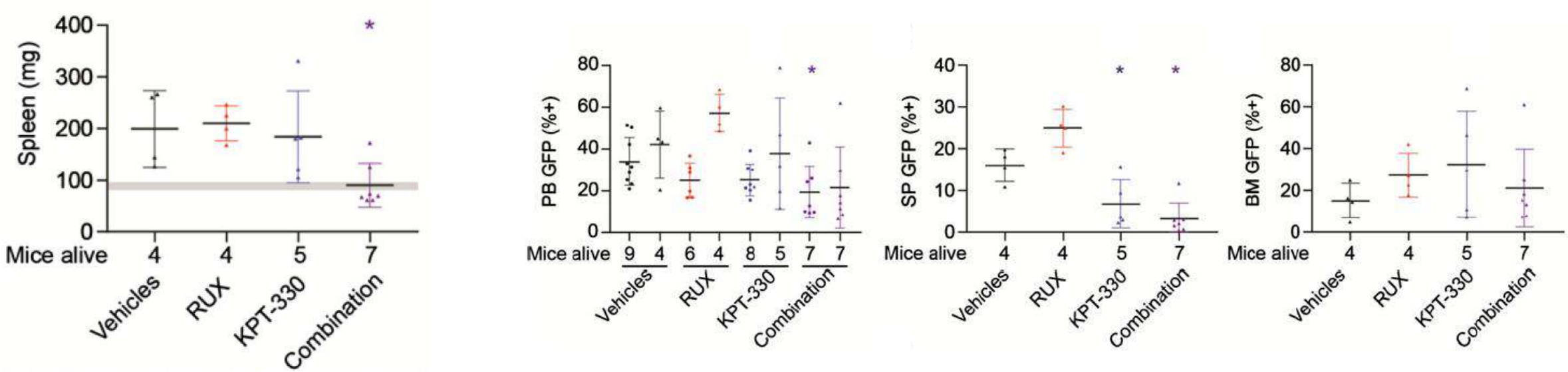






Yan et al Clin Cancer Res. 2019 Apr 1;25(7):2323-2335

Nuclear–Cytoplasmic Transport Is a Therapeutic Target in Myelofibrosis



Yan et al Clin Cancer Res. 2019 Apr 1;25(7):2323-2335

Selinexor Plus Ruxolitinib in JAK Inhibitor (JAKi)-Naïve Patients with Myelofibrosis

Phase 1 of XPORT-MF-034
Ruxolitinib + Selinexor

24 patients
- 10 received 40mg weekly
- 14 received 60mg weekly

Toxicity
Nausea (75%)
Fatigue (58%)
Anemia (54%)
Thrombocytopenia (54%)

SVR35
- 38% in 40mg
- 79% in 60mg

TSS50
- 10% in 40mg
- 58% in 60mg

JAK2 18 (75%)
CALR 5 (21%)
MPL (4%)

at week 24
38% has a ≥20% reduction in VAF

Tantravahi et al, Blood 142 (2023) 622–623

BCL2 / BCLxL - Navitoclax

Transform-1: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Phase 3 Study of Navitoclax in Combination with Ruxolitinib Versus Ruxolitinib Plus Placebo in Patients with Untreated Myelofibrosis

Phase 3 randomized RUX + NAV vs. Placebo

Intermediate-2 or high-risk MF

- Splenomegaly
- MF-related symptoms
- no prior JAK2i treatment

252 patients were enrolled

Table 2. Safety data

	NAV + RUX (N=124)	PBO + RUX (N=125)
Any AE	124 (100)	121 (97)
Any AE grade ≥3	105 (85)	87 (70)
Most common AEs (≥30% patients receiving NAV)		
Thrombocytopenia, any grade [grade ≥3]	112 (90) [63 (51)]	62 (50) [19 (15)]
Anemia, any grade [grade ≥3]	74 (60) [57 (46)]	61 (49) [49 (39)]
Diarrhea, any grade [grade ≥3]	42 (34) [6 (5)]	17 (14) [0]
Neutropenia, any grade [grade ≥3]	56 (45) [47 (38)]	7 (6) [5 (4)]
Any serious AE	32 (26)	40 (32)
All deaths	13 (10)	13 (10)
Deaths <30 days following last dose of study drug	6 (5)	5 (4)

SVR35

- 63.2% RUX + NAV
- 31.5% RUX + Placebo

TSS

- Minus 9.7 RUX + NAV
- Minus 11.1 RUX + Placebo

Pemmaraju et al Blood 142 (2023) 620–624

Fedratinib combinations

FEDORA: A phase II study to evaluate the tolerability, safety and activity of fedratinib combined with ropeginterferon alfa-2b in patients with myelofibrosis

FEDORA

Fedratinib

- JAK2 inhibitor
- Impressive clinical activity in trials of patients with primary and secondary MF.
- JAK2 inhibitors alone are unlikely to be curative and responses to JAK2 inhibition are highly heterogeneous

Ropeginterferon alfa-2b

- Can induce haematological responses in patients with pre-fibrotic primary MF.
- Combining a JAK2 inhibitor and an interferon may be more effective in the treatment of MF
- Haematopoietic cells are activated from quiescence by ropeginterferon alfa-2b which may render them more sensitive to JAK2 inhibition.

@CRCTU Cancer Research UK Clinical Trials Unit
TAP Bloodwise
CANCER RESEARCH UK
UNIVERSITY OF BIRMINGHAM

FEDORA: A phase II study to evaluate the tolerability, safety and activity of fedratinib combined with ropeginterferon alfa-2b in patients with myelofibrosis

FEDORA

Primary Objectives

Evaluate the tolerability of fedratinib and ropeginterferon alfa-2b combination therapy in patients with myelofibrosis

Secondary Objectives

- Evaluate safety and toxicity profile of combining fedratinib and ropeginterferon alfa-2b.
- Establish maximum ropeginterferon alfa-2b dose tolerated per patient when given in combination with fedratinib.
- Investigate the activity of combination therapy against splenomegaly and myelofibrosis related symptoms, quality of life, JAK2 clone size, and bone marrow fibrosis.

Cancer Research UK Clinical Trials Unit @CRCTU TAP Bloodwise CANCER RESEARCH UK UNIVERSITY OF BIRMINGHAM

Immune therapies

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

INCA033989 is a high affinity, fully human IgG1 selective for mutCALR

Functions as an antagonist to suppress TPO-R signalling induced by mutCALR.

Disrupts TPO-R oncogenic signalling by inhibiting mutCALR-dependent TPO-R dimerization

Binds $CD34^{+}$cells expressing mutCALR and inhibits mutCALR-driven activation of the JAK2/STAT pathway in a dose-dependent manner.

Competitive engraftment mouse model

- 10-week treatment with the antibody prevented the development of thrombocytosis by selectively decreasing mutCALR-positive platelet

Suppressed the mutCALR-induced accumulation of megakaryocytes in the bone marrow

Reis et al Blood (2022) 140 (Supplement 1): 9717–97

Discovery of JNJ-88549968, a Novel, First-in-Class CALRmutxCD3 T-Cell Redirecting Antibody for the Treatment of Myeloproliferative Neoplasms

Bispecific antibody targeting mutCALR

JNJ-88549968 elicited concentration-dependent cytotoxicity of patient-derived CALRmut CD34 + cell

JNJ-88549968 mediated robust *in vivo* efficacy in two independent CALRmut-positive xenograft murine leukemia model

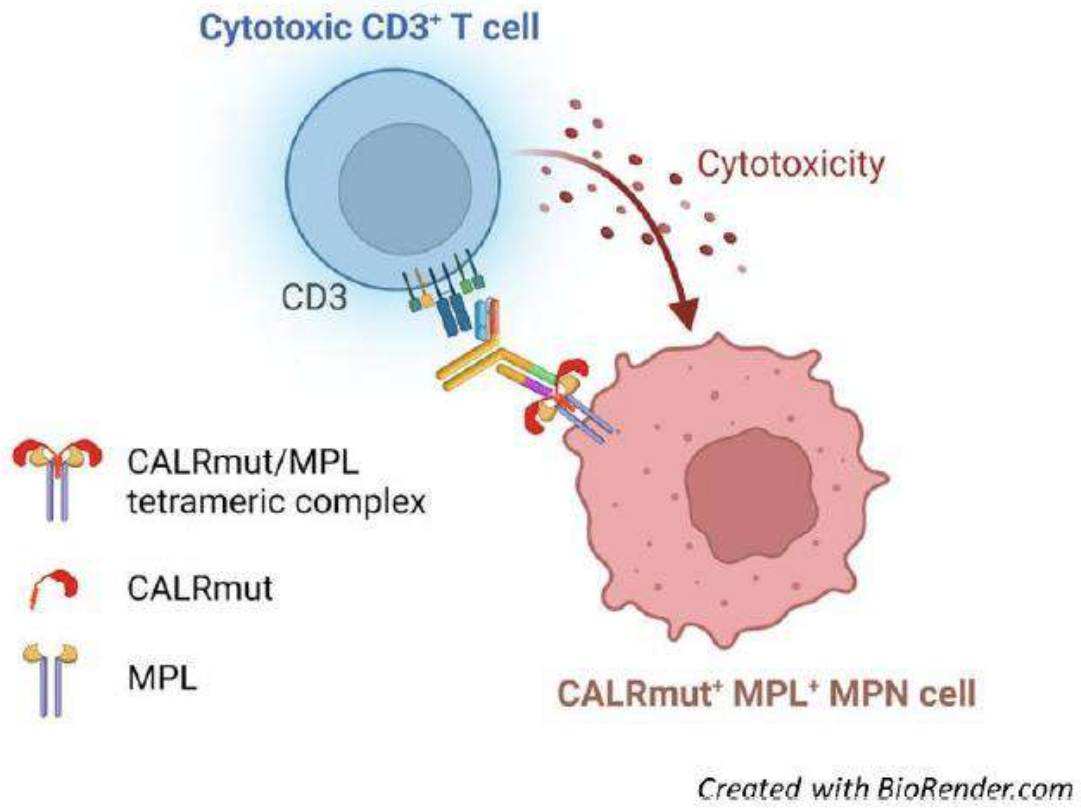


Figure 1

Kuchnio et al. Blood 142 (2023) 1777–1779

Novel therapies in myelofibrosis

BET inhibitors

LSD1 inhibitors

XPO1 / NCT inhibitors

BCL2/BCL_{XL}

Fedratinib / Interferon

Monoclonal antibodies CALRmut

Bispecific CALRmut-CD3

More disease modifying therapies

More clone targeting therapies

Thank you

- MPN team
  - Jane Apperley
  - Dragana Milojkovic
  - Simone Claudiani
  - Fiona Fernando
- Clinical Trials unit
  - Eleni Vourvou
- MRC-LMS at Imperial

a.innes@imperial.ac.uk