EHA-GBMTA-AHA Hematology Tutorial: New aspects in diagnostic choices and treatment options of hematological malignancies

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Session: Current approaches to management of MPN

October 2024, Dr Patrick Harrington

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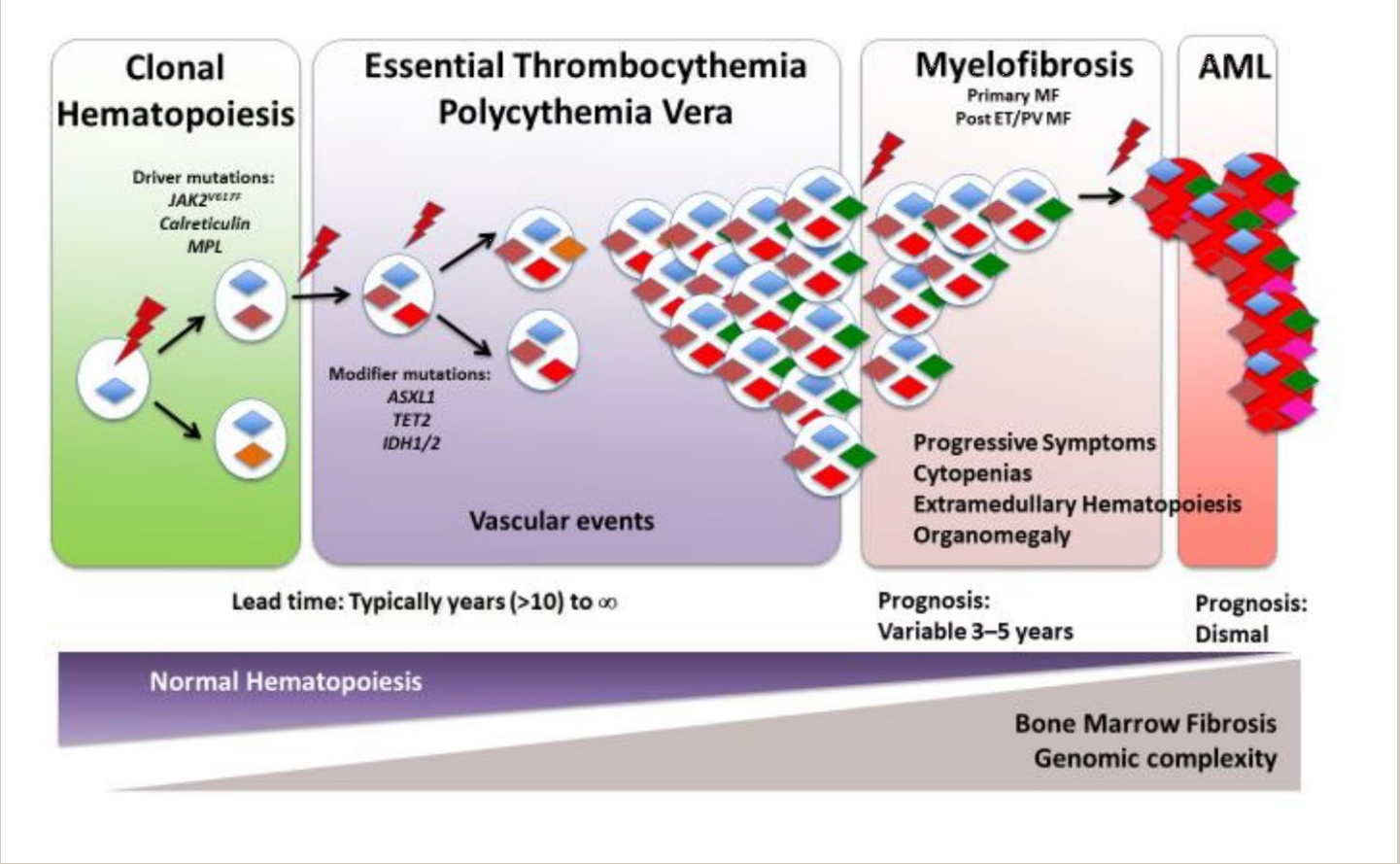
Disclosures:

Honoraria: GSK, Incyte, Novartis

Research Funding: GSK, Incyte, Novartis, BMS, Constellation, AOP

Introduction

- Polycythaemia vera
  - Disease stratification
  - Molecular monitoring
  - Current treatments
- Myelofibrosis
  - Prognosis
  - JAK inhibitors
  - Combination Therapies



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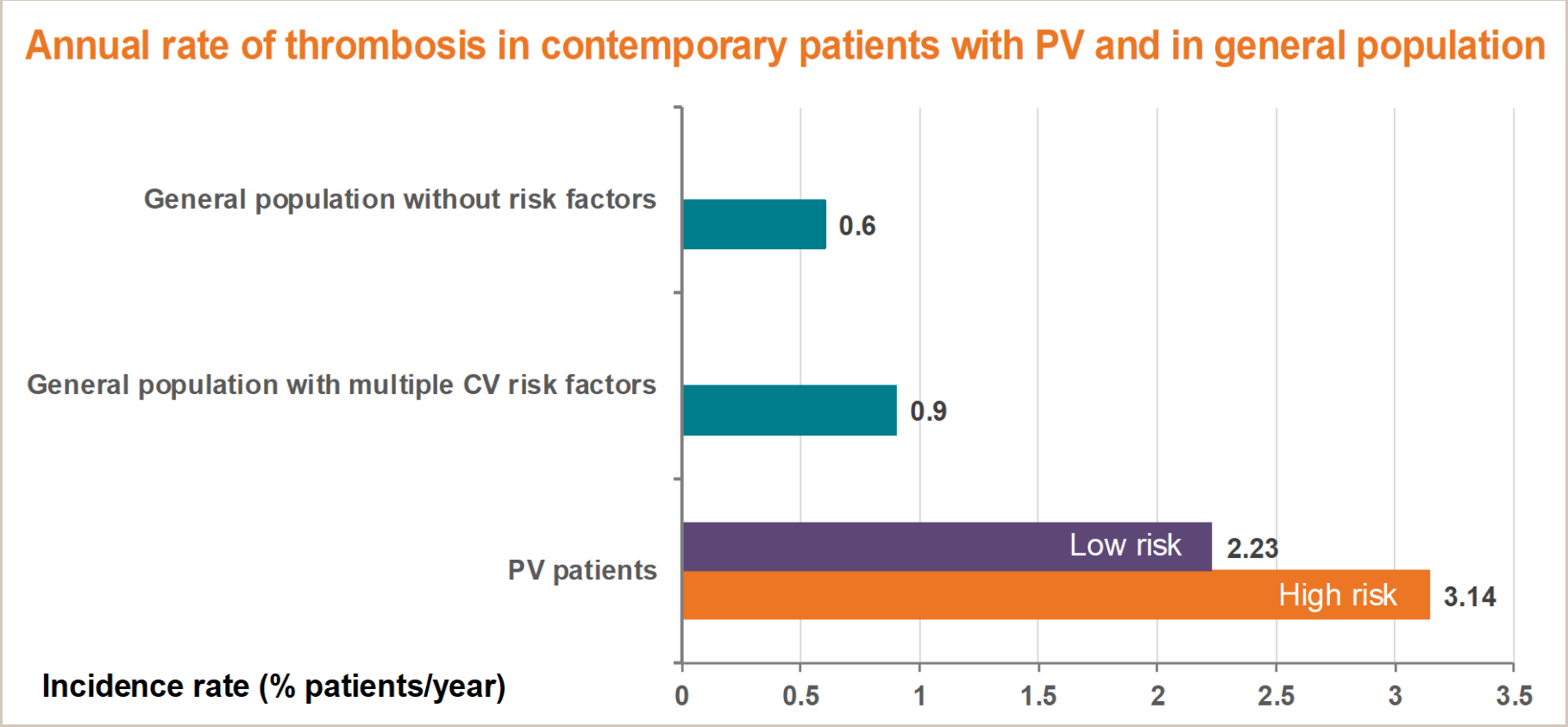
Diagnostic Criteria:

WHO 2022[1]	ICC 2022[2]	BSH guidelines 2018[3]
Major criteria: • Elevated Hb (>16.5 g/dL in males; >16.0 g/dL in females) or elevated HCT (>49% in males; >48% in females) • BM biopsy: hypercellularity with trilineage grown (panmyelosis), including erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes • *JAK2* or *JAK2* exon 12 mutation **Minor:** • Subnormal EPO level	**Major criteria:** • Elevated Hb (>16.5 g/dL in males; >16.0 g/dL in females) or elevated HCT (>49% in males; >48% in females) or increased RBC mass (>25% above mean normal predicted value) • BM biopsy: age-adjusted hypercellularity with panmyelosis, including prominent erythroid, granulocytic, and increase in pleomorphic mature megakaryocytes without atypia • *JAK2*V617F or *JAK2* exon 12 mutation **Minor:** • Subnormal EPO level	***JAK2*-positive PV** A1. High HCT (>0.52 in males; >0.48 in females) or raised RBC mass (>25% above predicted) A2. Mutation in JAK2 ***JAK2*-negative PV** (A1–4, + another A or 2B) A1. Raised red cell mass (>25% above predicted) or HCT ≥0.60 in males/≥0.56 in females A2. Absence of *JAK2* A3. No secondary cause of erythrocytosis A4. BM histology consistent with PV A5. Palpable splenomegaly A6. Presence of an acquired genetic abnormality (excluding *BCR-ABL1)* in the haematopoietic cells B1. Thrombocytosis B2. Neutrophil leucocytosis B3. Radiological evidence of splenomegaly B4. Low serum EPO

Barbui T, et al. *Blood Cancer J* 2018;8(2):15;
Virchows Arch 2023;482(1):53–68;
McMullin MF, et al. *Br J Haematol* 2019;184(2):176–191.

‘Low Risk’ Polycythaemia Vera



Crodel C, et al. J Cancer Res Clin Oncol 2022;148(10):2693–2705

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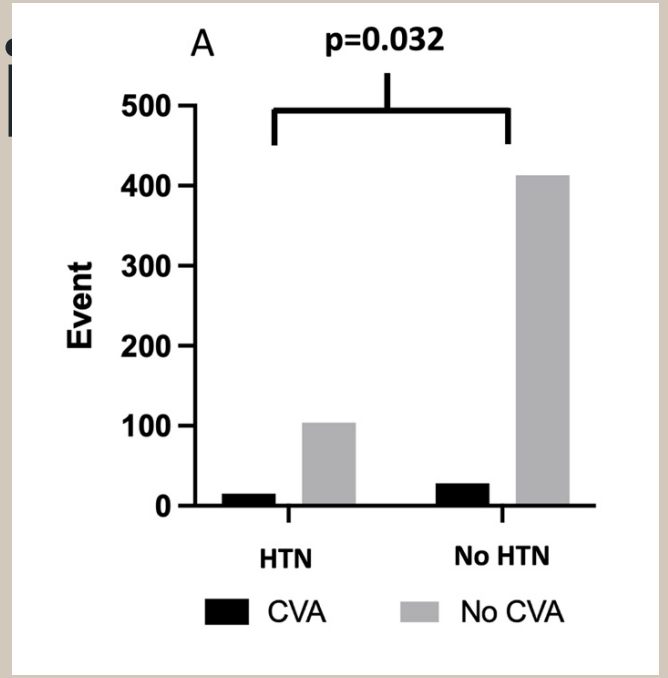
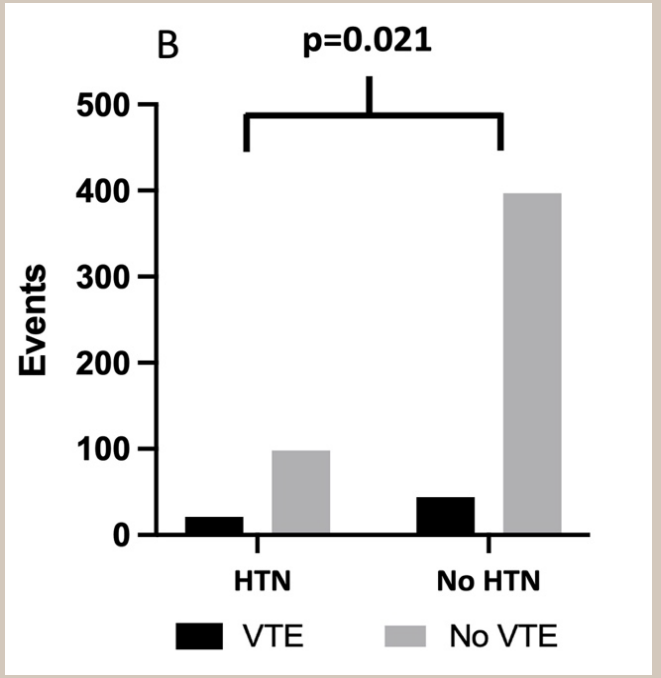
Natural Language Processi

PV – 360 patients, 11250 documents

ET – 560 patients, 12905 documents

Type of thrombosis	ET (560 patients) n (%)	PV (360 patients) n (%)	p
Deep venous thrombosis	8 (1.4)	10 (2.8)	0.15
Pulmunary embolism	10 (1.8)	10 (2.8)	0.314
Myocardial infarction	20 (3.6)	11 (3.1)	0.673
Cerebrovascular accident	43 (7.7)	51 (14.2)	0.002
Portal vein thrombosis	7 (1.3)	18 (5)	<0.001
Cerebral venous thrombosis	6 (1.1)	1 (0.3)	0.177
Thrombosis, NOS	45 (8)	70 (19.4)	<0.001
Venous thromboembolism	65 (11.6)	84 (23.3)	<0.001
Overall thrombotic events	112 (20)	126 (35)	<0.001



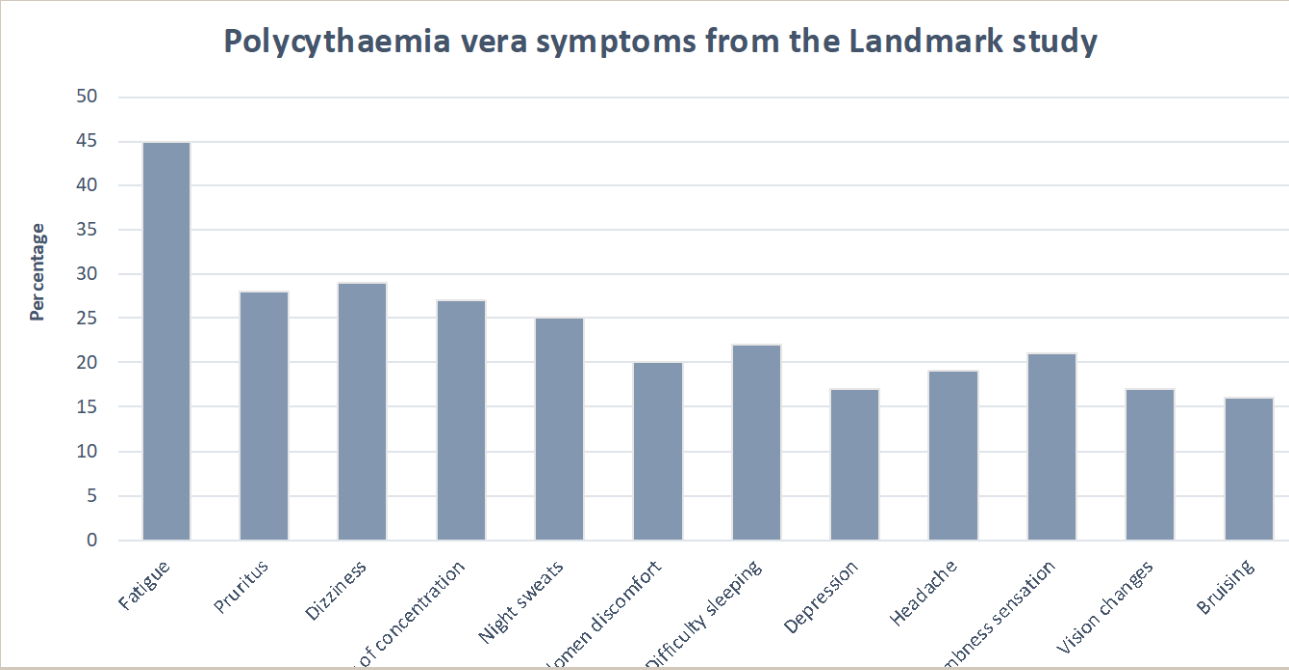


Duminuco et al, Hemasphere 2024;8:e143

Symptom Burden in PV

72% of PV patients report QoL affected by symptoms

- Potential for impact with therapies
- Need for improved monitoring



Harrison, Ann Hematol. 2017 Oct;96(10):1653-1665

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Real-World Evaluation of Risk Factors for Disease Progression in Patients with Polycythaemia Vera

High risk PV based on thrombotic risk and previously defined as:

- Age >60/65 yrs
- Prior thrombotic events

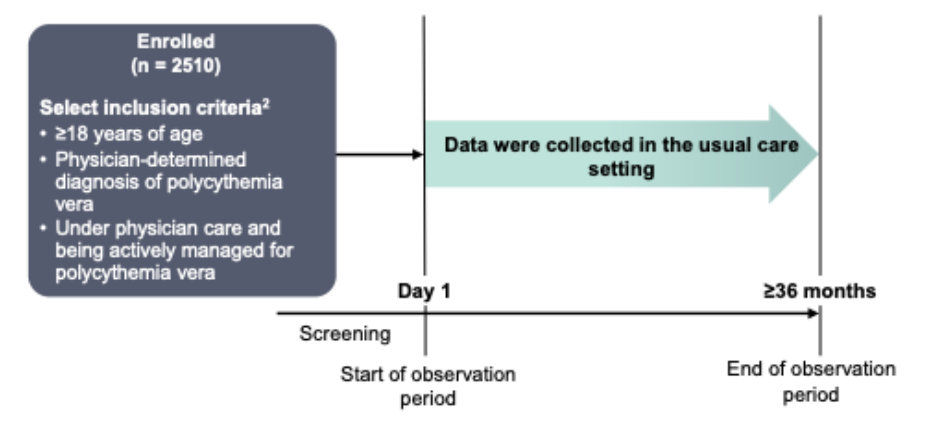
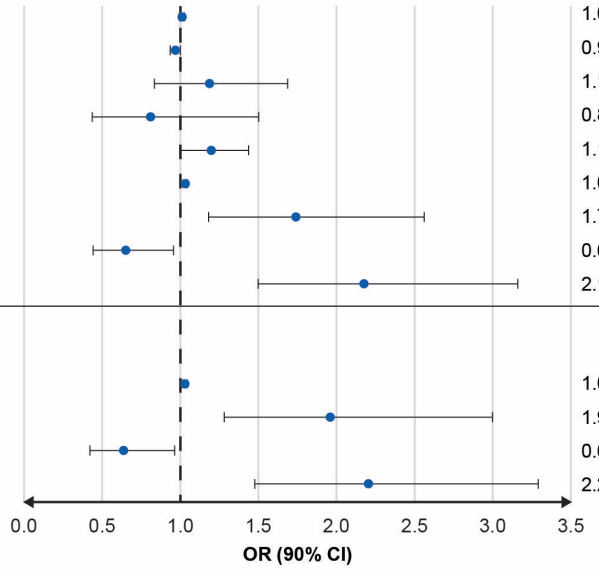


Figure 1. Associations Between Patient Characteristics and PV Progression

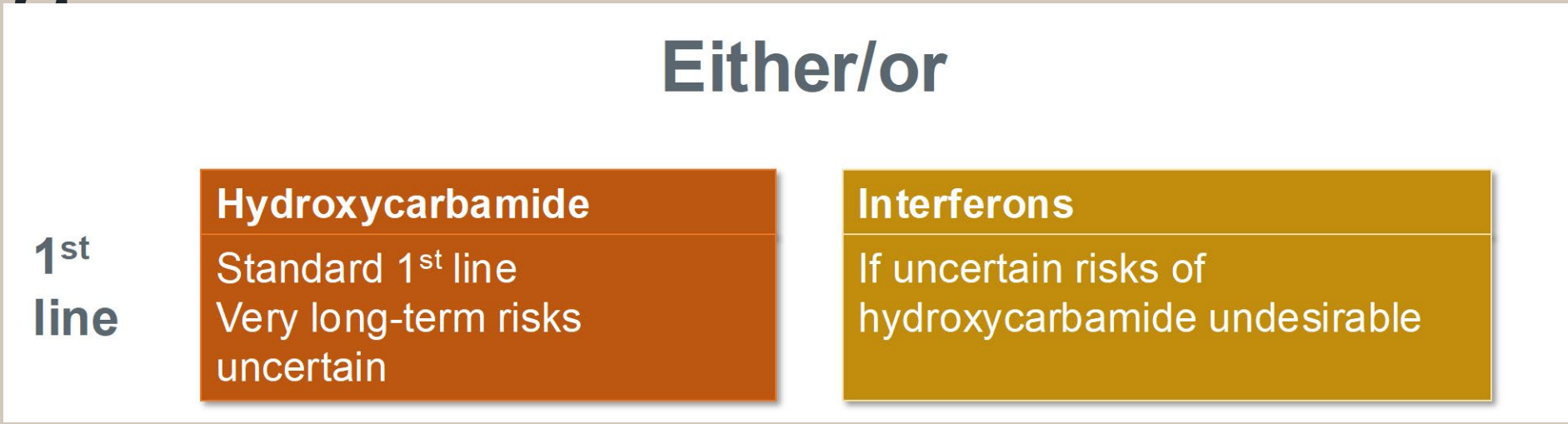
Analysis	OR (90% CI)	*P* Value
Univariate logistic regression on PV disease progression		
Age, y	1.012 (0.997-1.027)	0.1323
BMI, lb/in²	0.968 (0.936-1.001)	0.0580
Sex (female vs male)	1.187 (0.835-1.688)	0.3397
White (yes vs no)	0.809 (0.436-1.502)	0.5015
Charlson Comorbidity Index	1.198 (0.998-1.437)	0.0520
Time from PV diagnosis to enrollment	1.032 (1.020-1.045)	**<0.0001**
History of TE (yes vs no)	1.740 (1.182-2.562)	**0.0050**
HCT (>0.45 vs ≤0.45 L/L)	0.650 (0.442-0.956)	**0.0288**
WBC (>11 vs ≤11×10⁹/L)	2.176 (1.498-3.161)	**<0.0001**
Multivariate logistic regression on PV disease progression with stepwise model selection		
Time from PV diagnosis to enrollment	1.030 (1.016-1.044)	**<0.0001**
History of TE (yes vs no)	1.960 (1.281-2.998)	**0.0019**
HCT (>0.45 vs ≤0.45 L/L)	0.637 (0.421-0.964)	**0.0330**
WBC (>11 vs ≤11×10⁹/L)	2.205 (1.477-3.292)	**0.0001**



Significant values are indicated in bold font.

Grunwald et al. ASH 2023, Abstract 385

Cytoreduction in Polycythaemia Vera



Strongly consider for 'low-risk' PV with:

- WBC >11-15 x 10^9/L
- Cardiovascular risk factors
- Symptoms unresponsive to other measures eg antihistamines
- Venesections > 4/year or untolerated or problematic iron deficiency
- Platelets > 1000 x 109/L
- JAK2 VAF >50%

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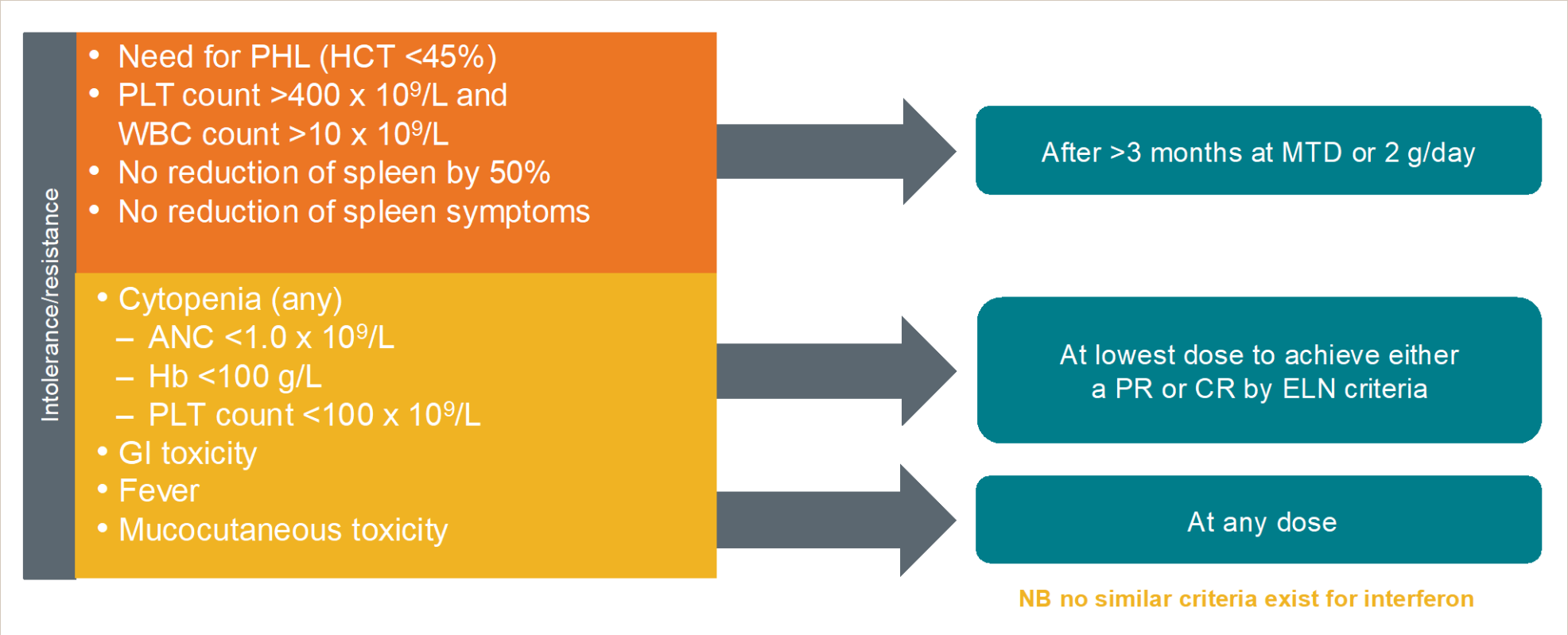
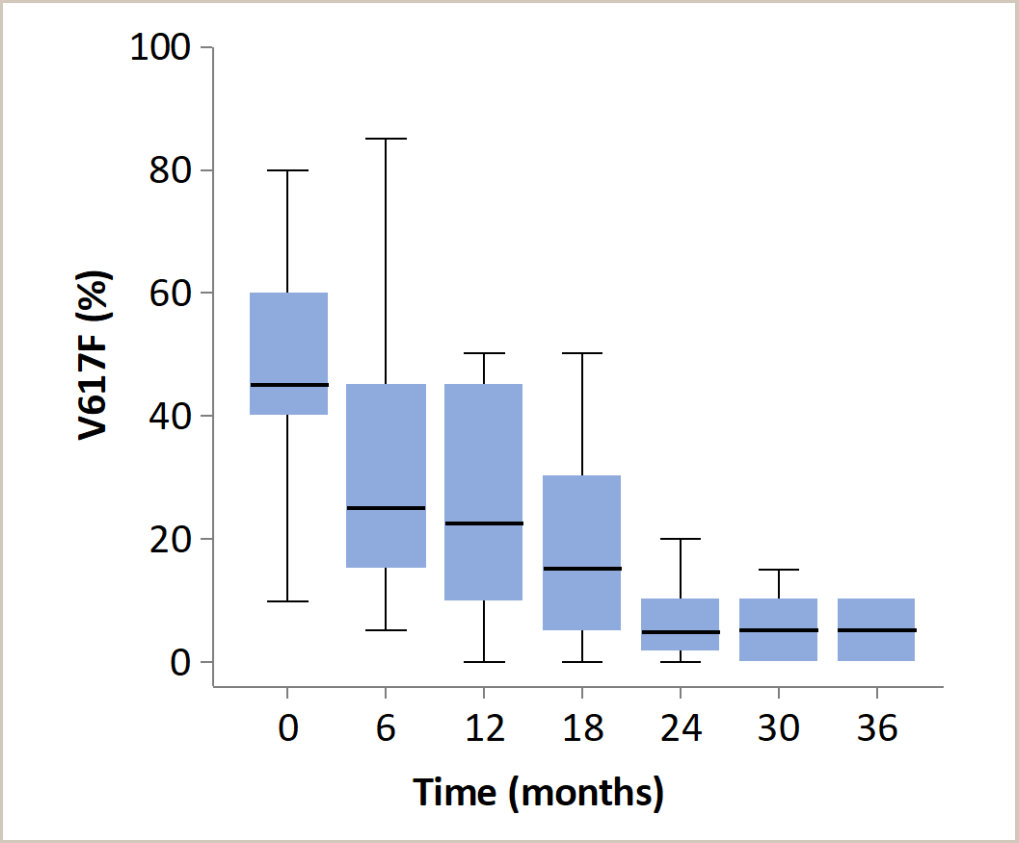
Hydroxycarbamide Resistance

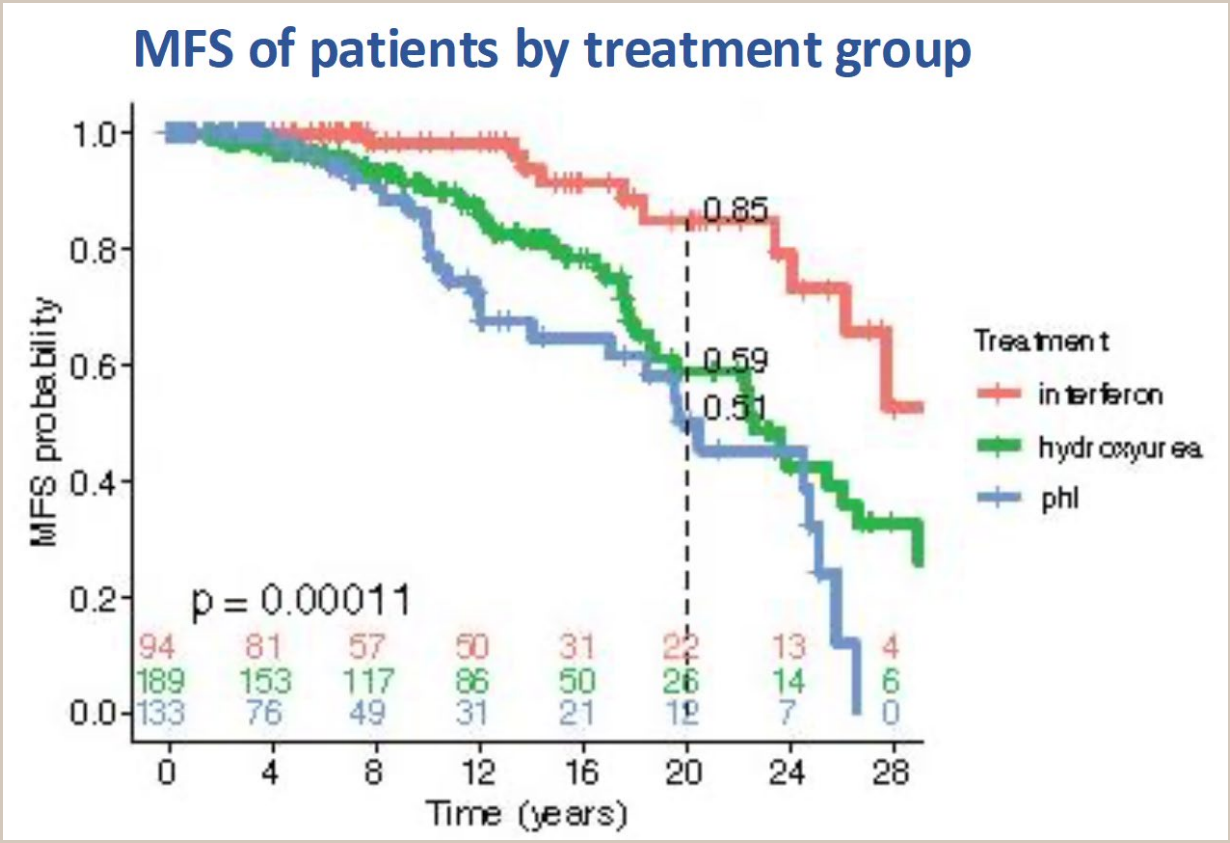
ELN Consensus Criteria:



Barosi G, et al. Br J Haematol 2010;148(6):961–963

Pegylated IFNa and Response





Kiladjian JJ, et al. Blood. 2008;15:3065-72.
Abu-Zeinah G, et al. Blood 2020;136 (Supplement 1):31–32

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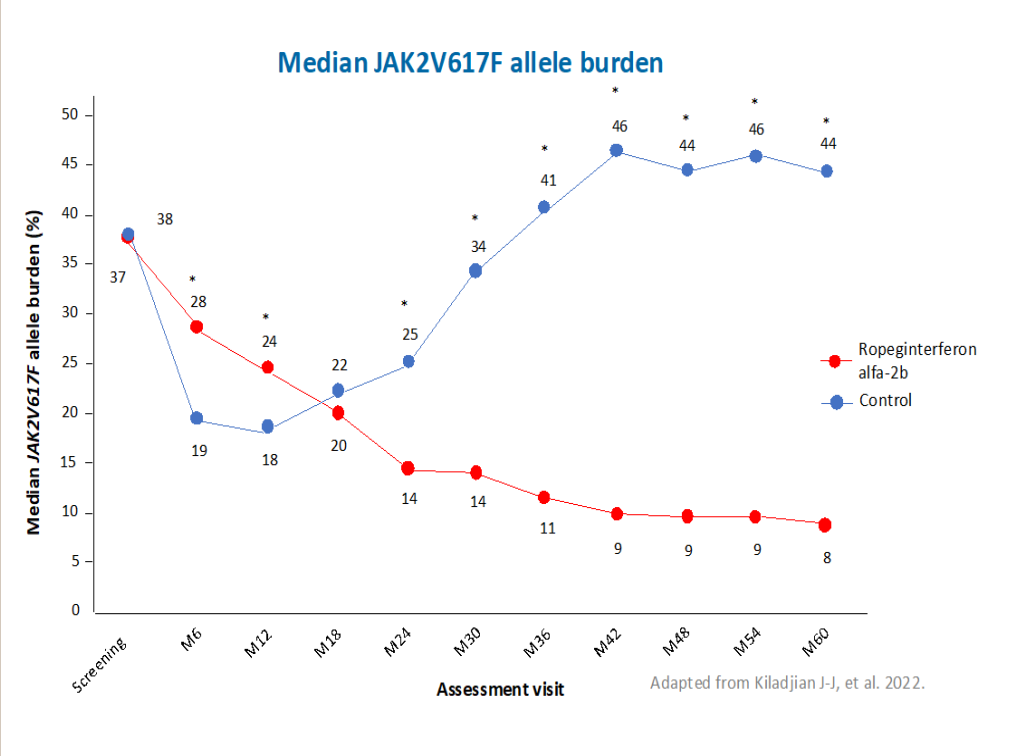
Ropeginterferon α-2b: PROUD-PV

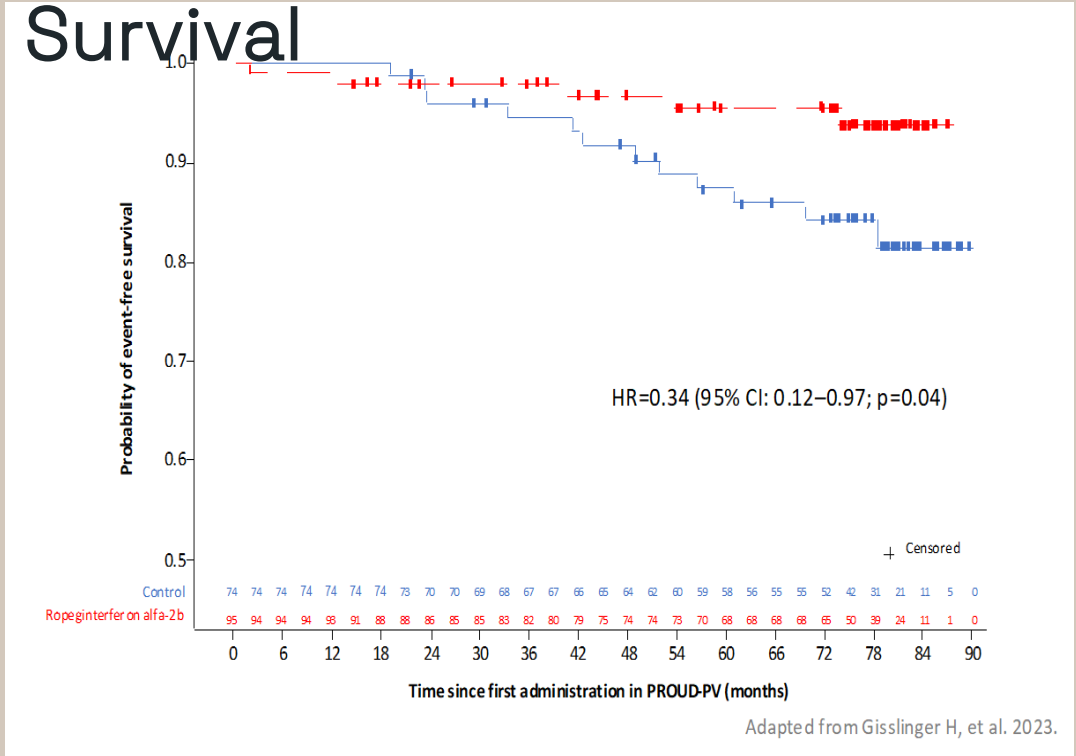
PROUD PV study – Ropeginterferon alpha 2b vs BAT including HC naïve and suboptimal responders

88% of BAT group received hydroxycarbamide

Molecular Response



Event Free Survival



Kiladjian J-J, et al. Leukemia 2022;36:1408–1411.

RESPONSE Study

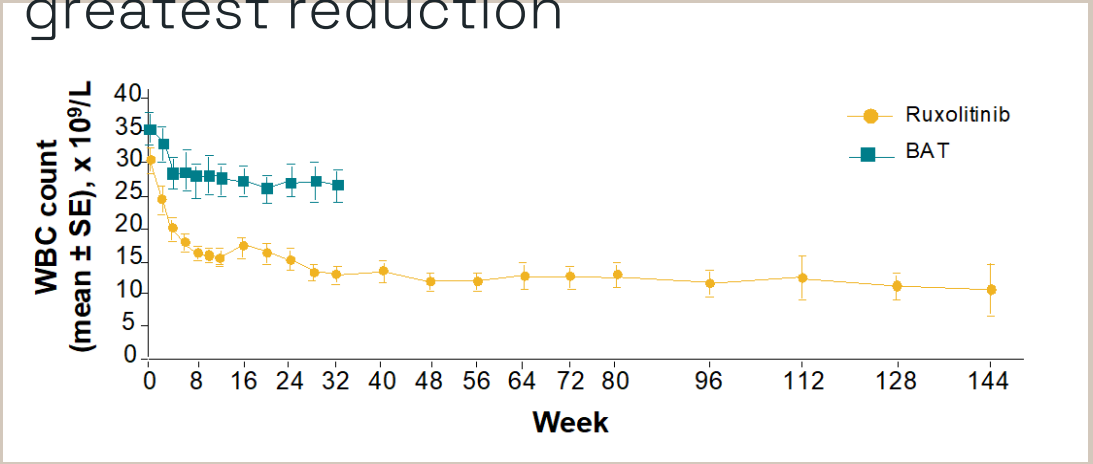
Ruxolitinib vs BAT in HC resistant or intolerant PV patients with splenomegaly

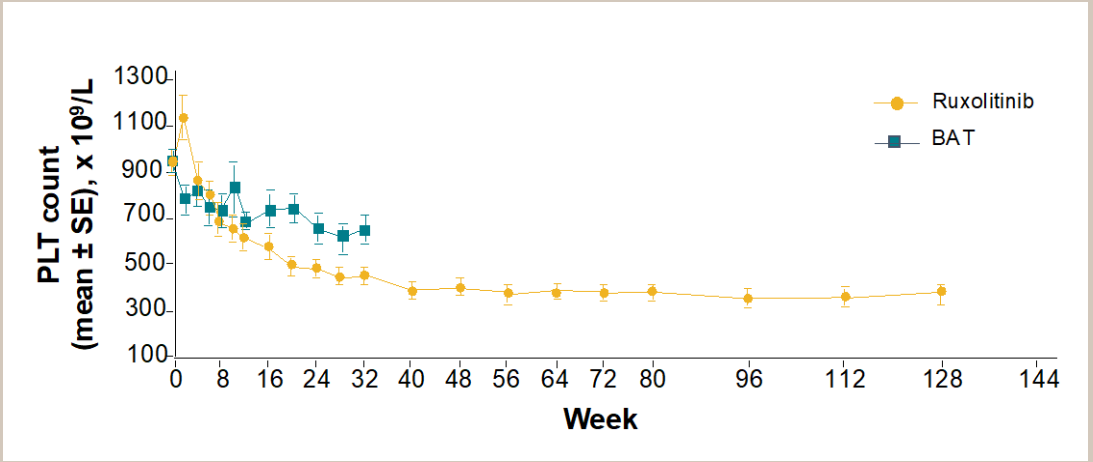
- Primary end-point: HCT control and 35% spleen response

Primary outcome achieved in 22.7% with RUX *vs.* 0.9% with BAT:

- hematocrit control, 60.0% *vs.* 18.8%;
- spleen response, 40.0% *vs.* 0.9%)

Patients with highest baseline WBC and platelet count showed greatest reduction



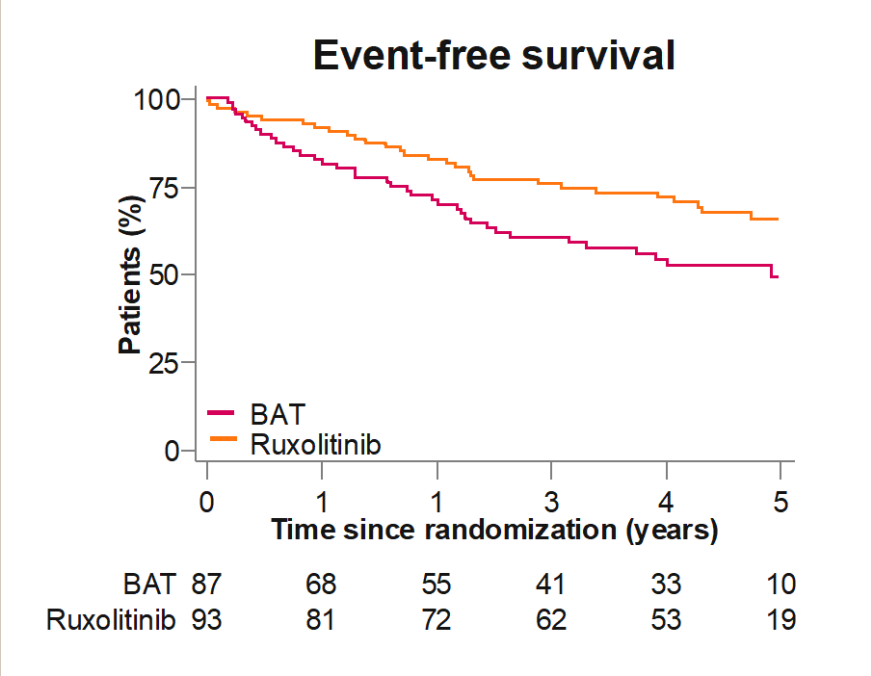


Kiladjian J-J, et al. Lancet Haematol 2020;7(3):e226–e237

MAJIC-PV

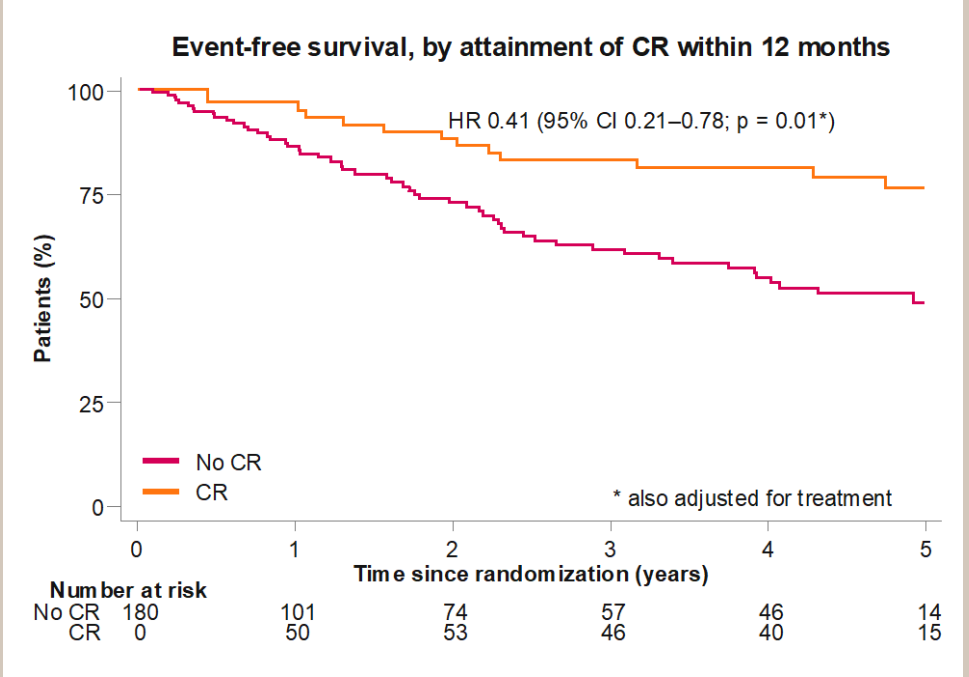
RUX vs BAT in 2nd line for high-risk PV

Primary end point: EFS (haemorrhage, thrombosis, transformation or death)



Ruxolitinib associated with 42% reduction in risk of events cf. BAT

Attaining CR within 12 months is associated with 59% reduction in EFS



Harrison et al., J Clin Oncol, 2023 Jul 1;41(19):3534-3544

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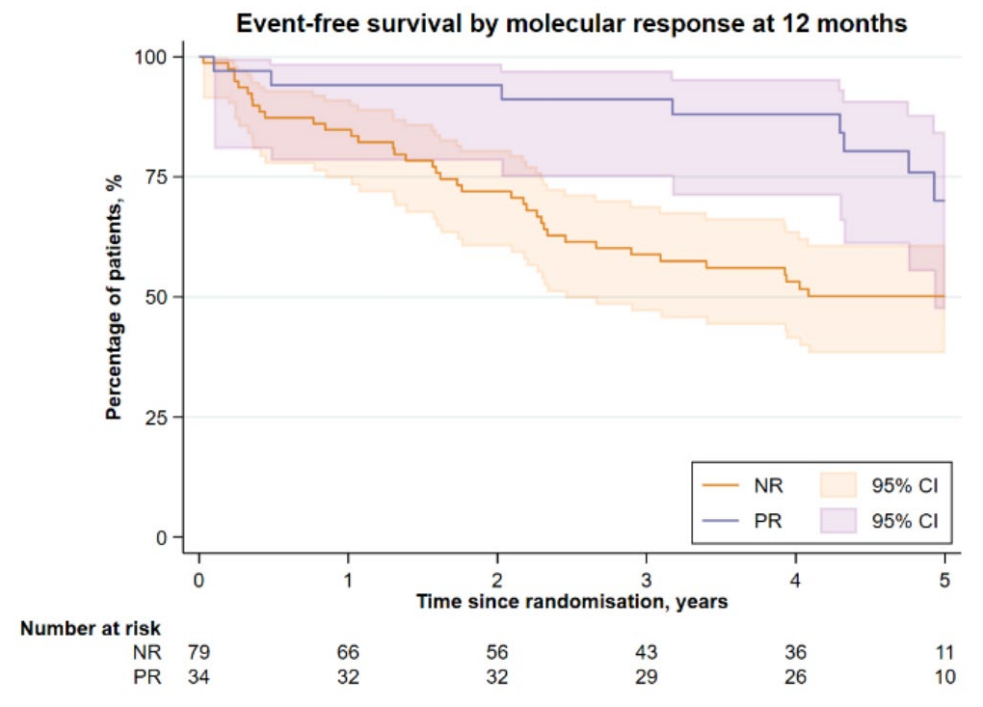
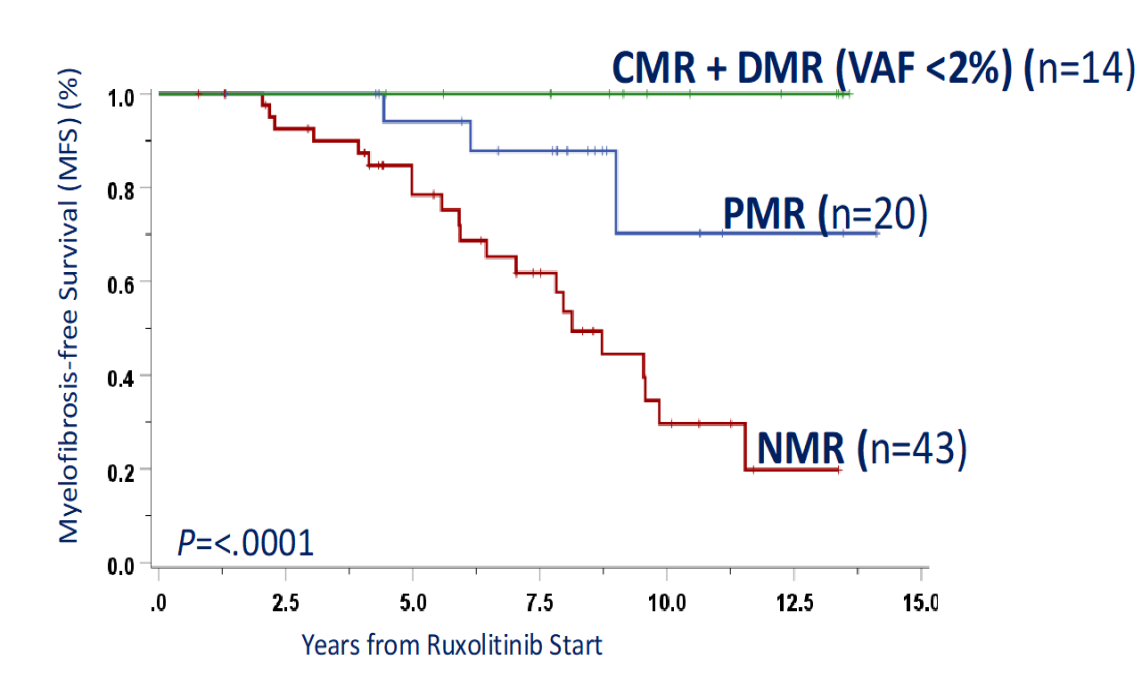
Improved Outcomes with Molecular Response in Ruxolitinib treated PV

MAJIC-PV: >50% response



MFS by molecular response



Harrison et al., J Clin Oncol, 2023 Jul 1;41(19):3534-3544
Gugielmelli et al. ASH 2022

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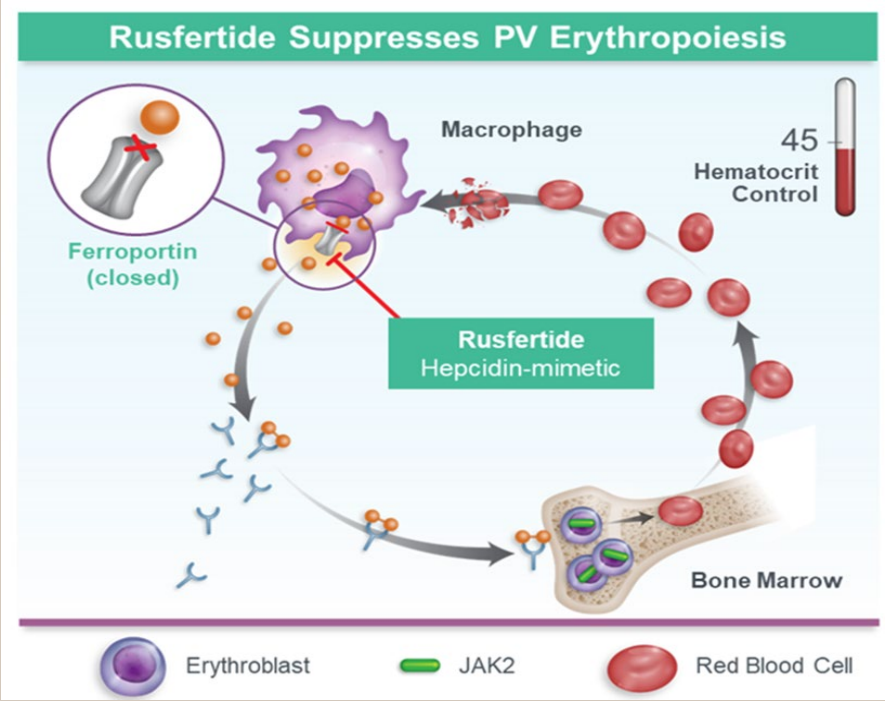
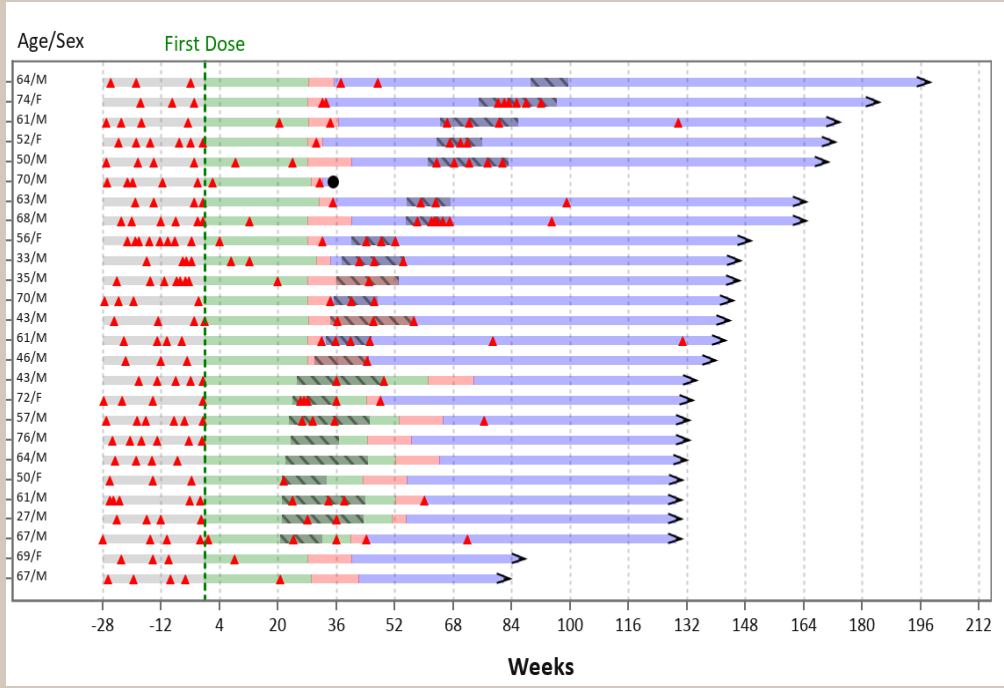
Rusfertide Decreased Frequency of Venesection

Eligibility: PV patients with ≥3 therapeutic phlebotomies in 28-week period prior to enrollment

With or without concurrent cytoreductive therapies





Kremanskaya et al. N Engl J Med 2024;390:723-735

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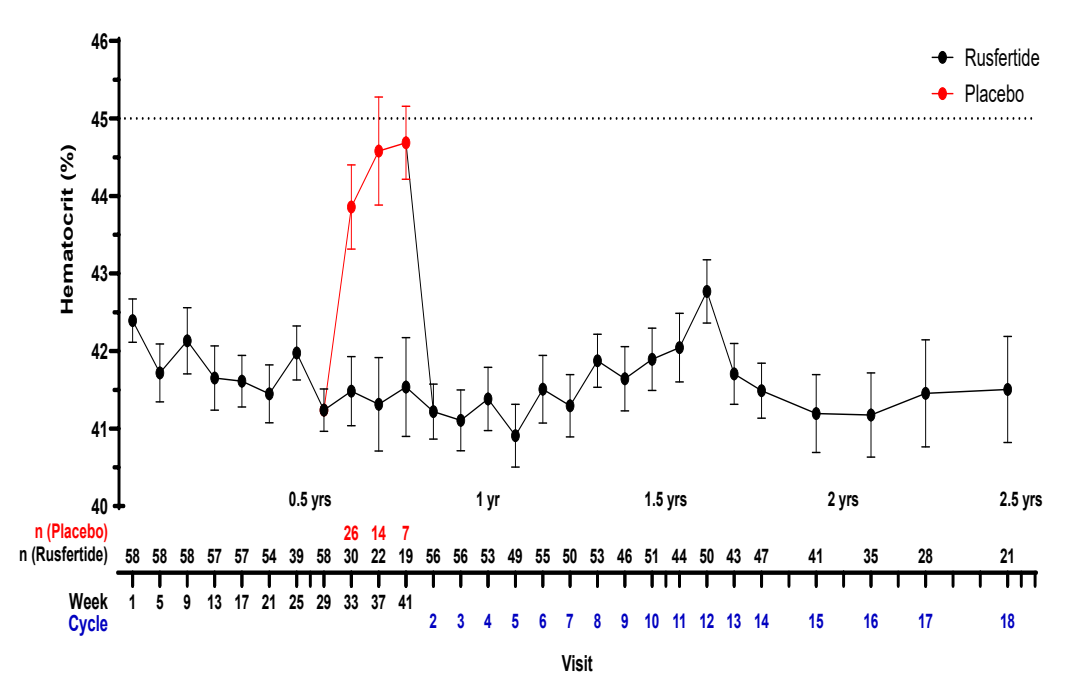
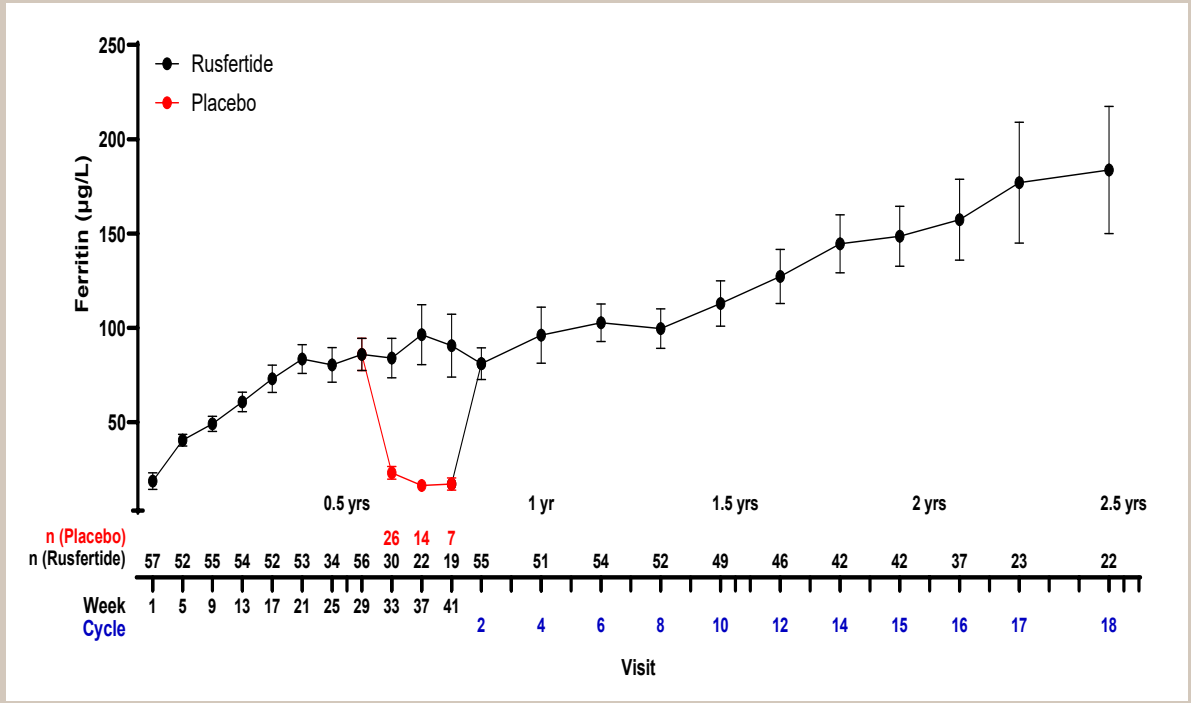
Rusfertide Provided Durable Control of the Hematrocrit



Rusfertide Resulted in Normalization of Serum Ferritin



Kremanskaya et al. N Engl J Med 2024;390:723-735

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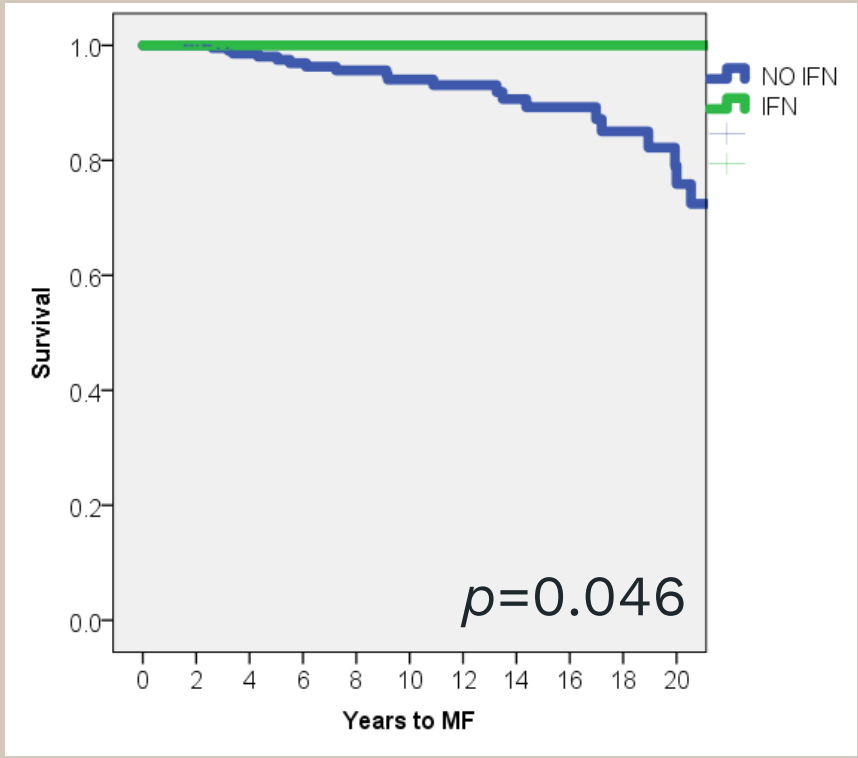
Young MPN patients: MFS

Impact of treatment in ET/PV in those aged <25 yrs at diagnosis

All (n=348), first line	10 yrs MFS	20 yrs MFS
Interferon	100%	100%
Hydroxyurea	93% (86-99%)	74% (57-92%)
Anagrelide	92% (82-100%)	73% (40%-100%)
No cytoreduction	94% (88-100%)	74% (47-100%)

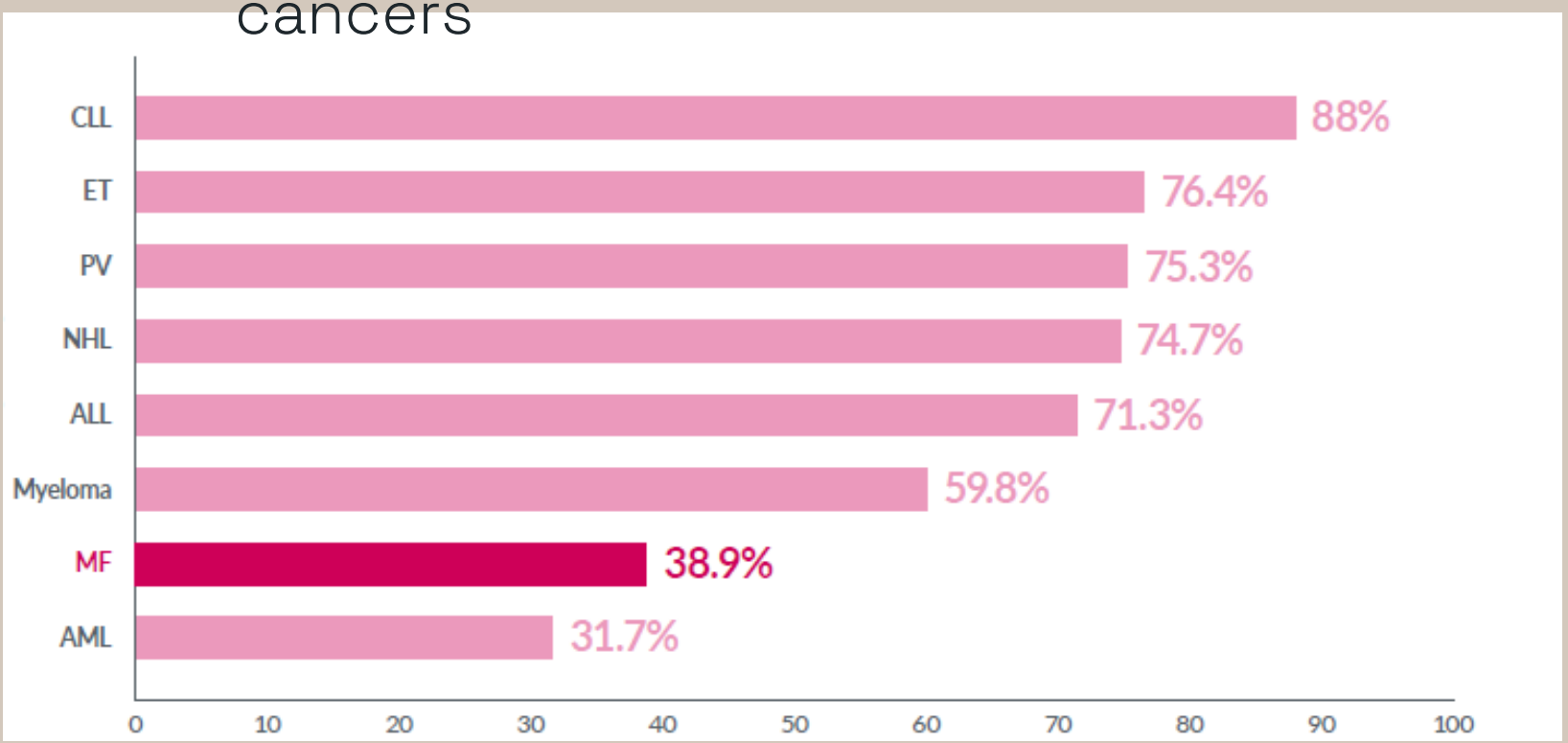


IFN significantly reduces the risk of progression to sMF

Beauverd et al. ASH 2023 - Abstract #748

Myelofibrosis: an area of unmet need

5-year survival rates in selected cancers



Brunner AM, et al. Leuk Lymph. 2016;57:1197–1200

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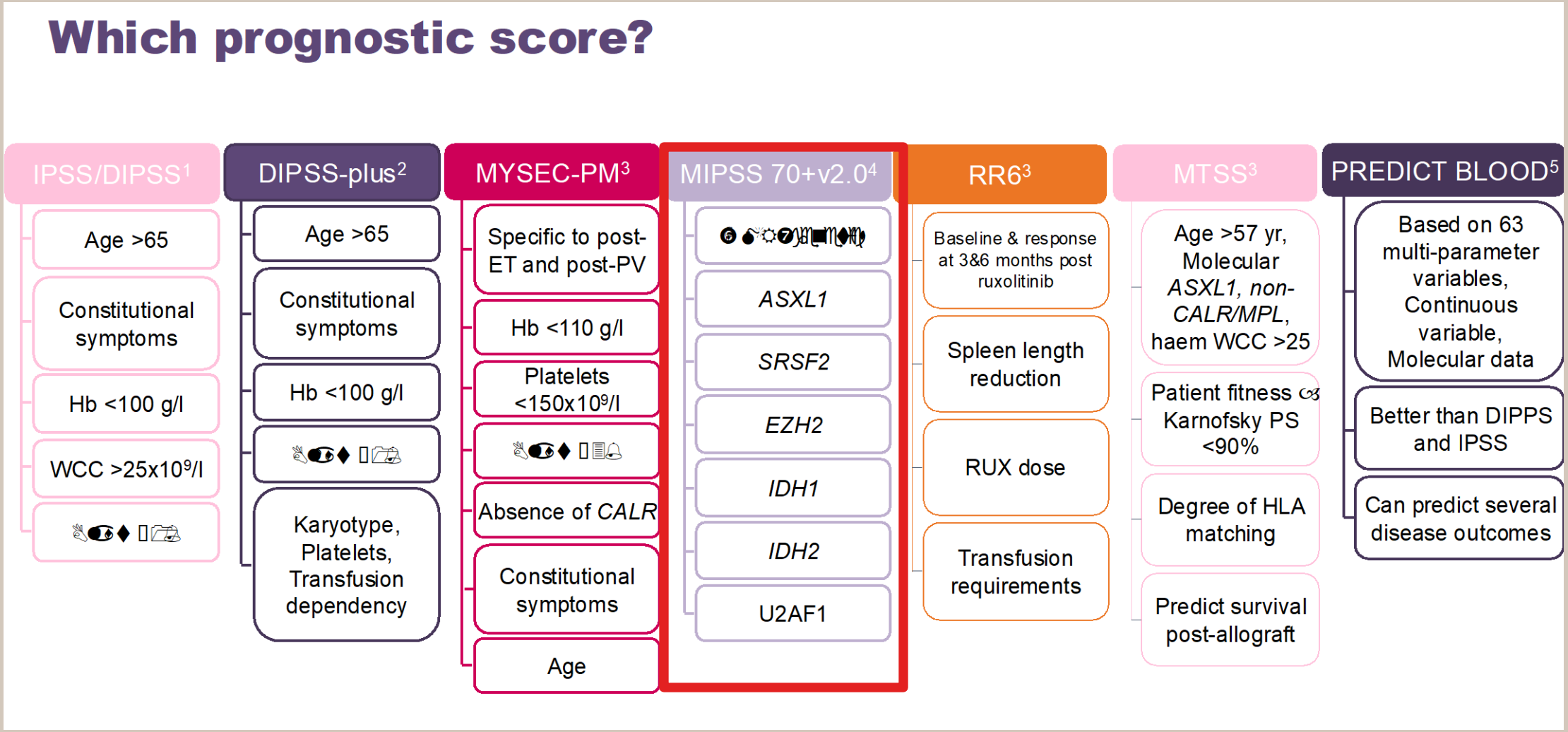
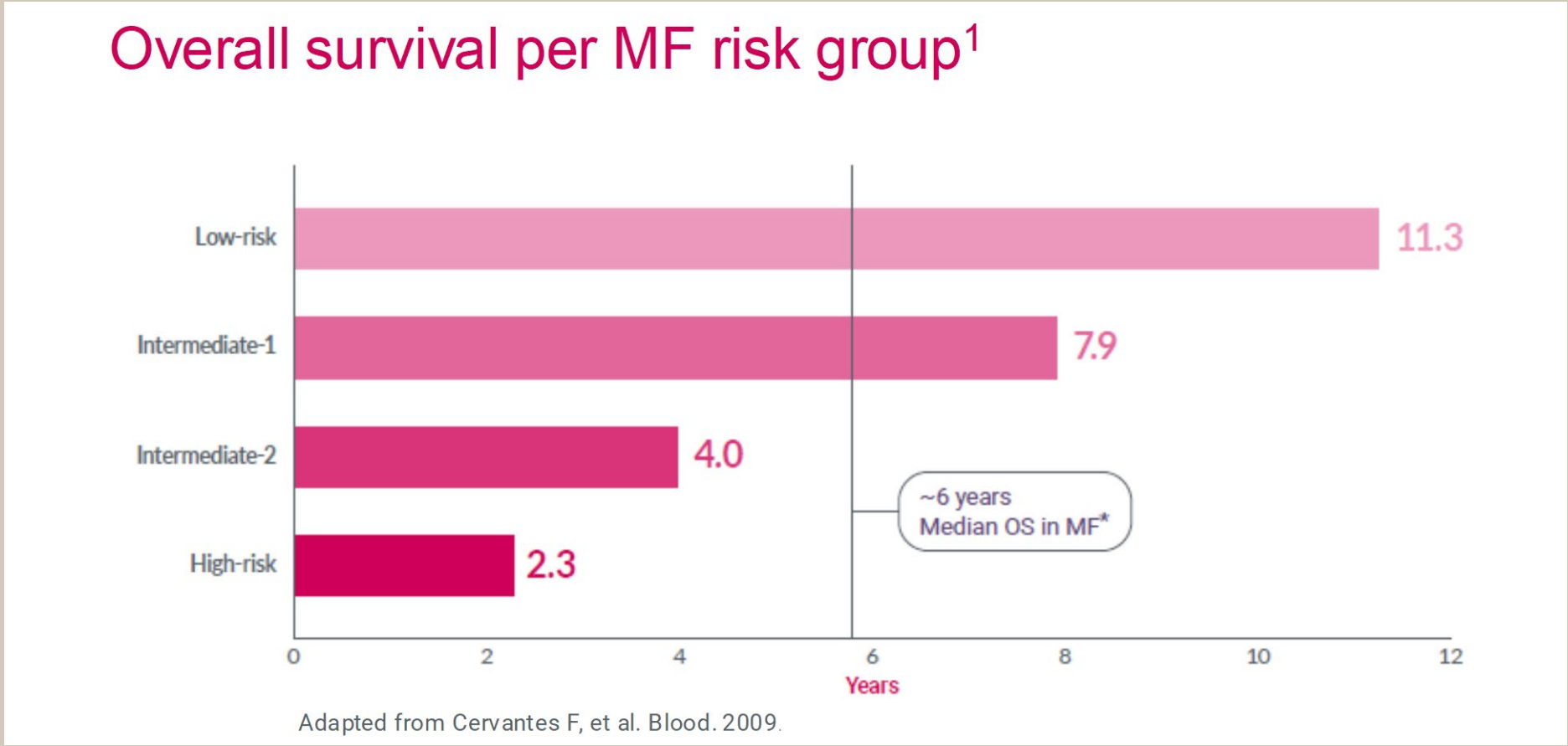
Myelofibrosis Prognostication



Duminuco A, et al. *J Clin Med*. 2023;12:2188

Myelofibrosis Survival



Cervantes F, et al. Blood. 2009;113:2895–2901

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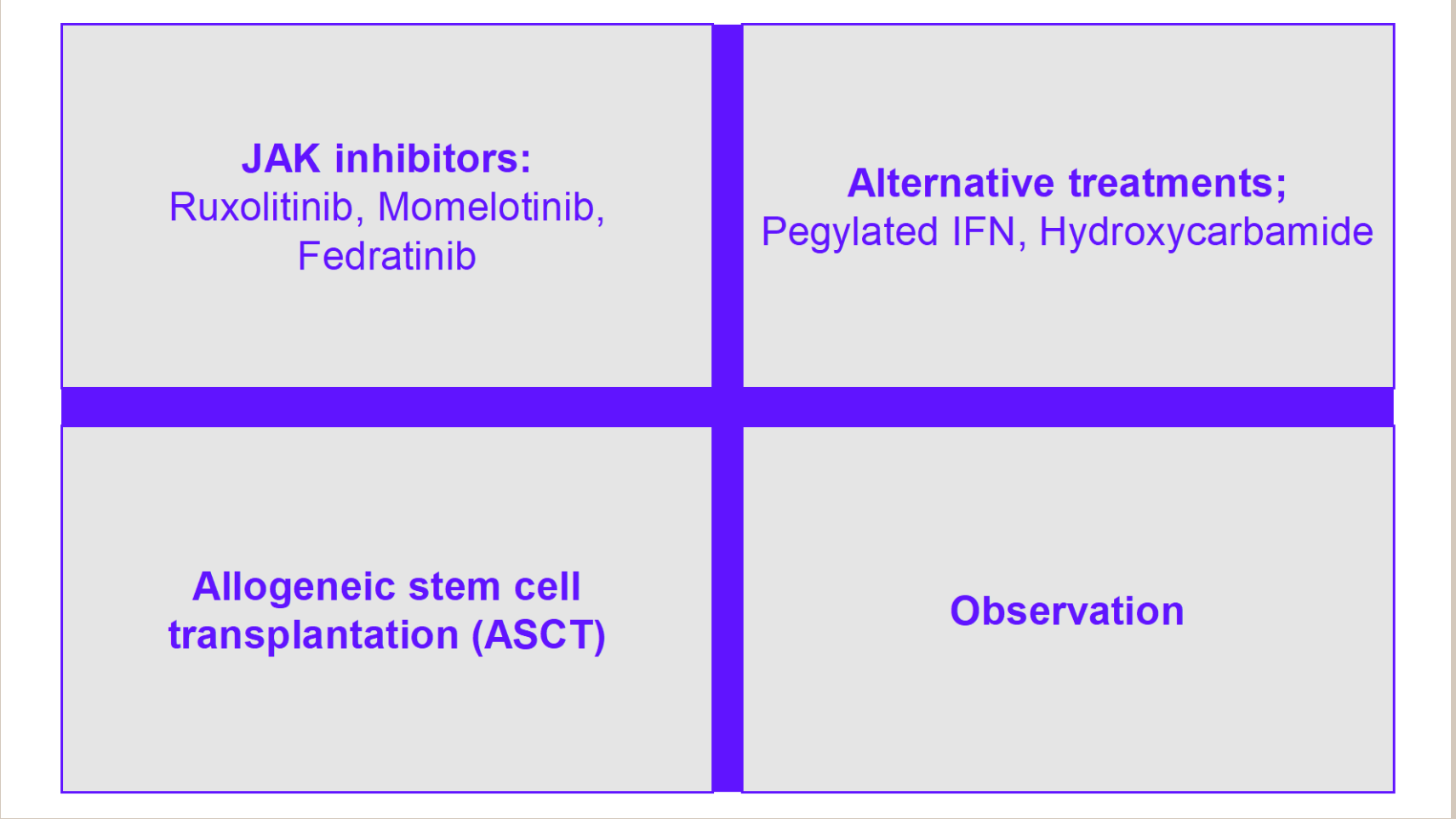
Treatment Options in Myelofibrosis



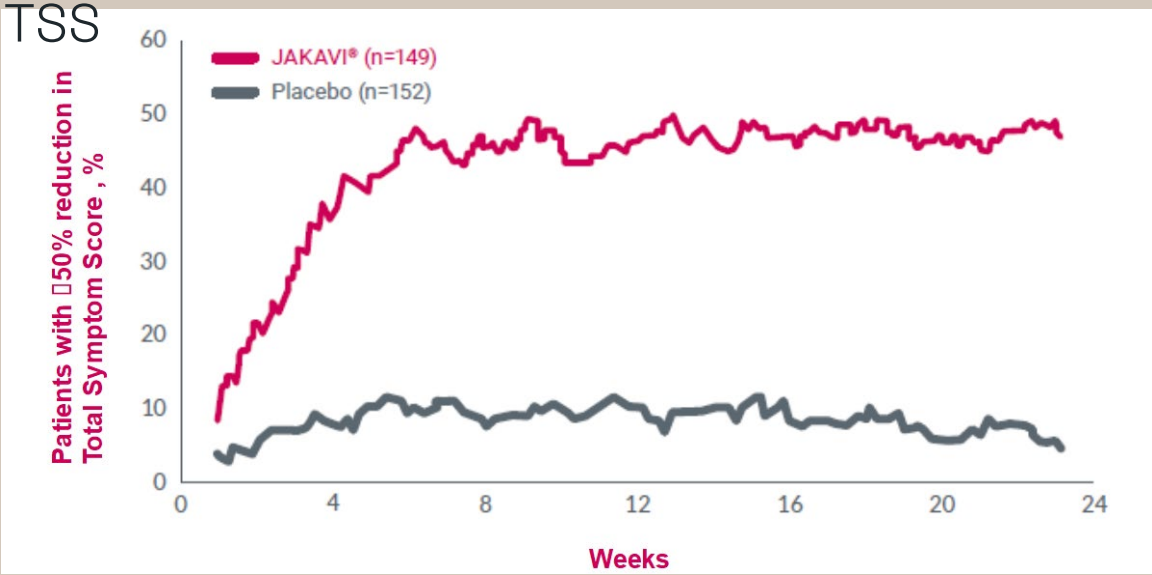
McLornan DP *et al*. *Br J Haematol*. 2024;204(1):136-150

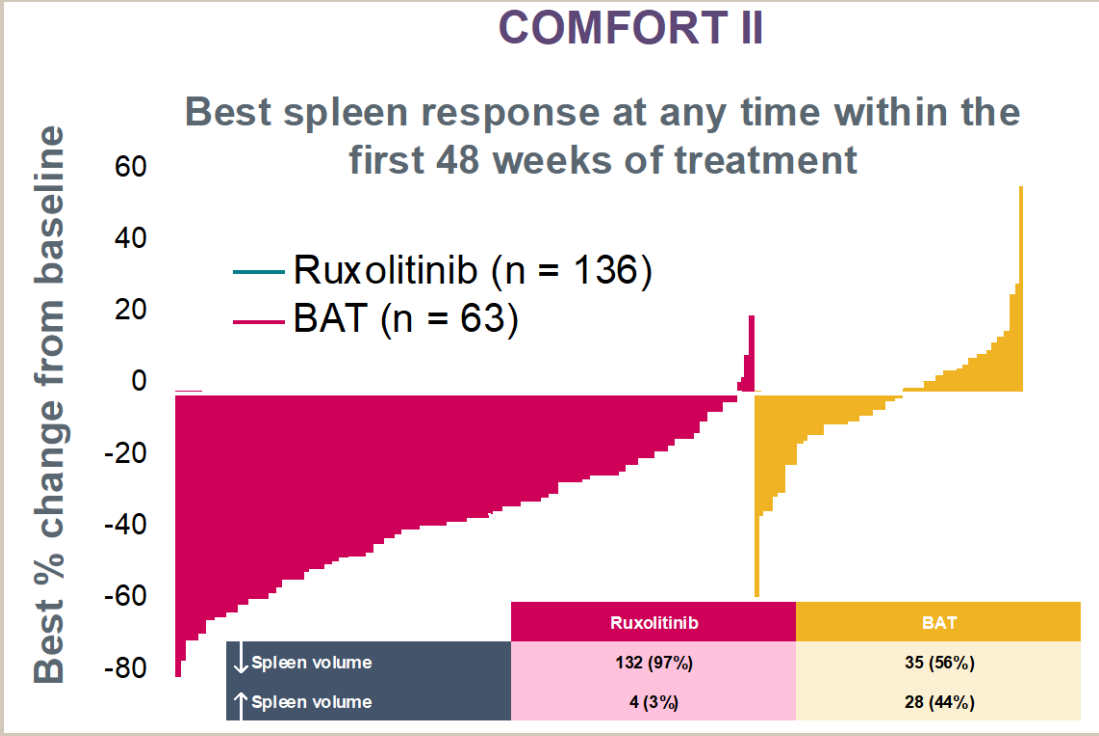
Ruxolitinib

JAK 1 and 2 inhibitor
Evaluated in:

- COMFORT-1 vs placebo
- COMFORT-2 vs BAT

COMFORT-1 – >50% Reduction in TSS





Significant reduction in spleen volume observed

Primary end point >35% reduction in spleen volume

- Achieved in 41% with RUX vs 0.7 % with BAT

Harrison C, et al. *N Engl J Med*. 2012;366:787–798.
Verstovsek S, et al. *N Engl J Med*. 2012;366:799–807

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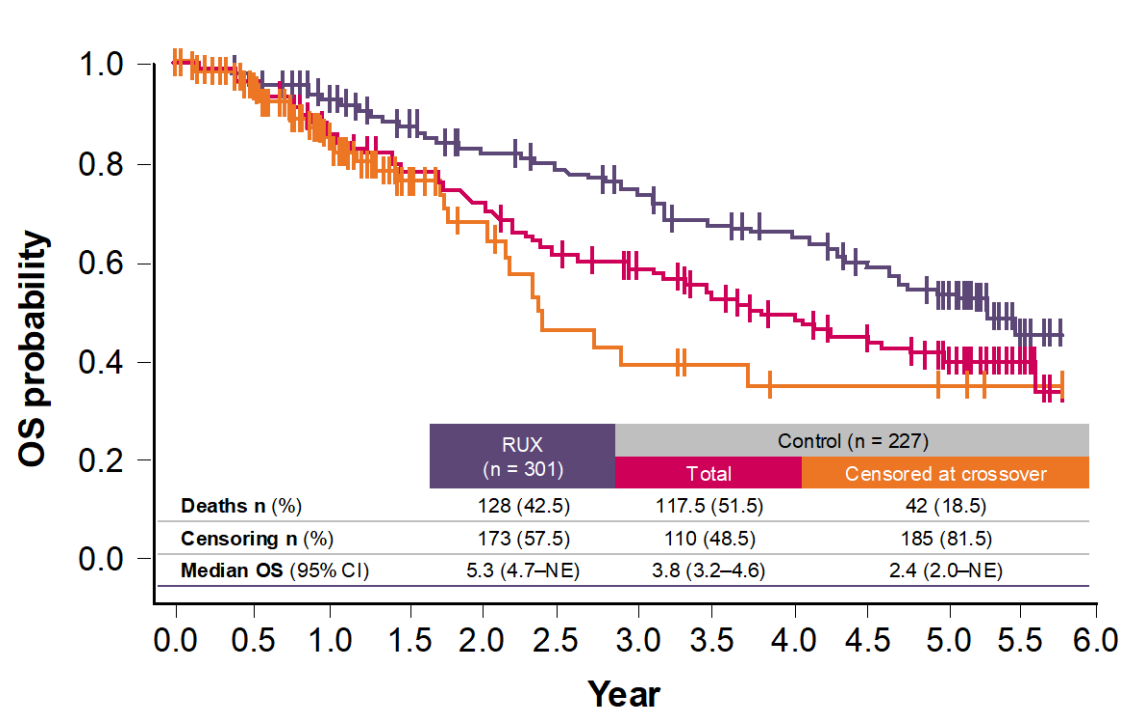
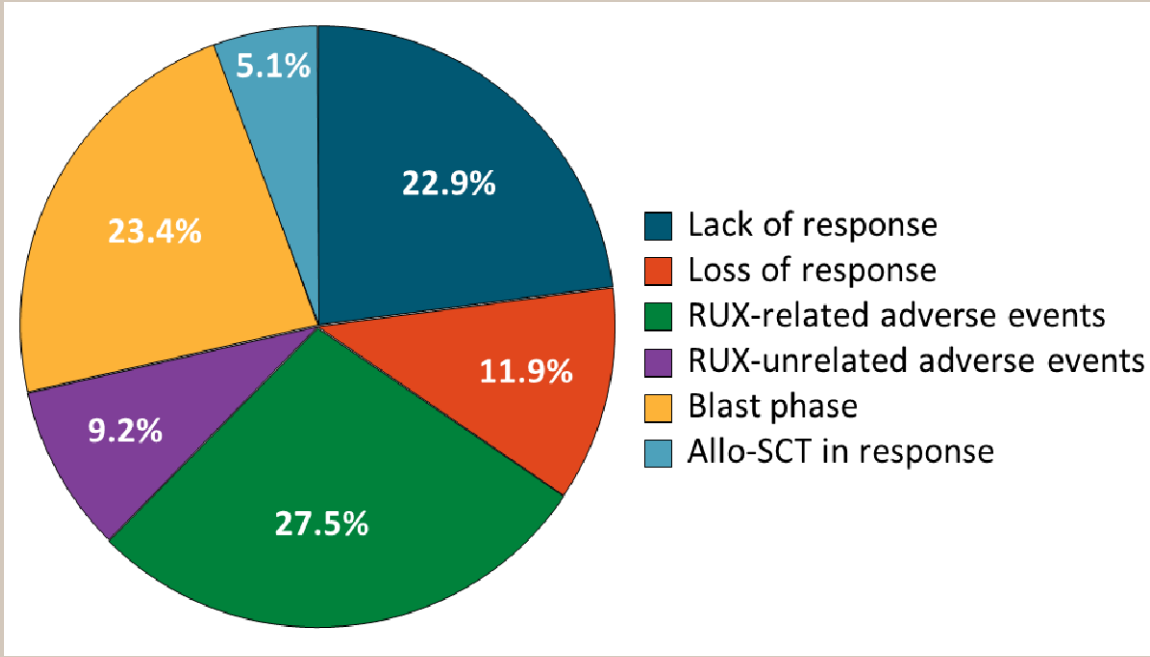
Ruxolitinib long term outcomes

Pooled data from COMFORT 1 and 2 suggests improved OS with RUX

- Median OS 5.3 vs 3.8 years





However RUX resistance/intolerance is common: around 3-5 years - intolerance due to infections, non melanomatous skin cancer

Palandri F, et al. *Cancer*. 2020;126:1243–1252
Verstovsek S, et al. *J Haematol Oncol*. 2017;10:156

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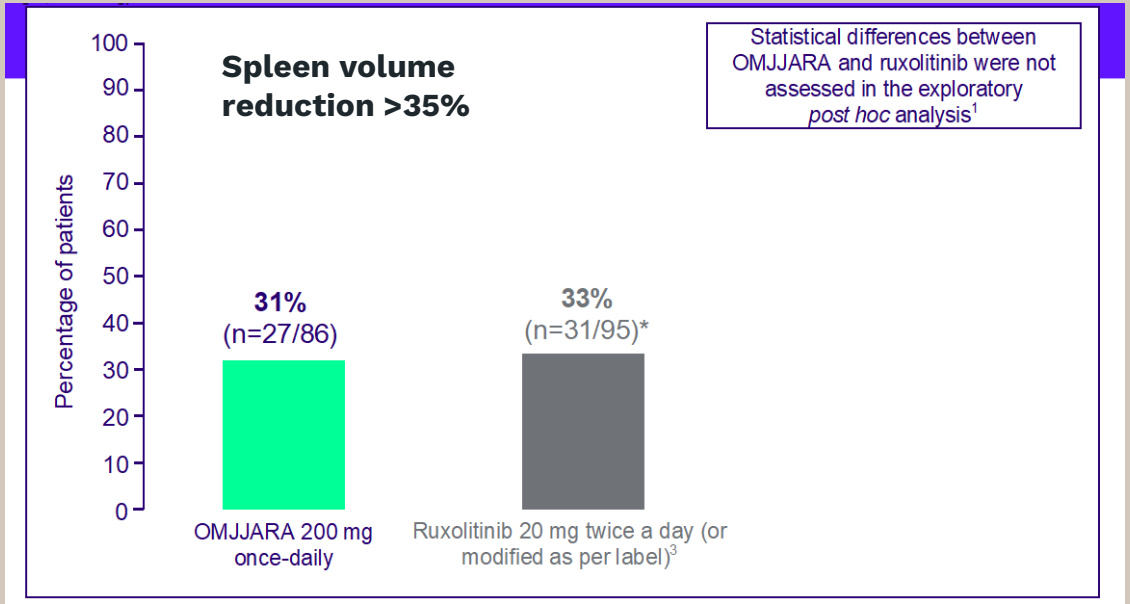
Momelotinib

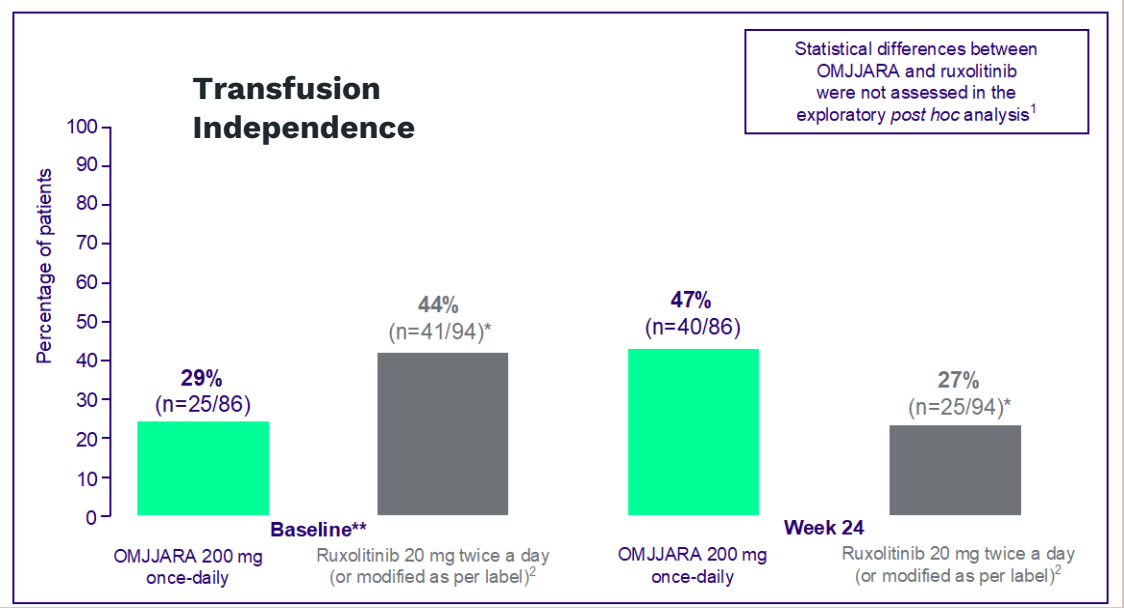
SIMPLIFY-1 trial – momelotinib vs ruxolitinib in treatment naïve MF with splenomegaly

Met primary endpoint (non-inferiority):
Spleen volume reduction ≥35% from baseline at week 24 met (top)

Secondary end point of TSS>50 not met

Post hoc analysis revealed significant improvement in

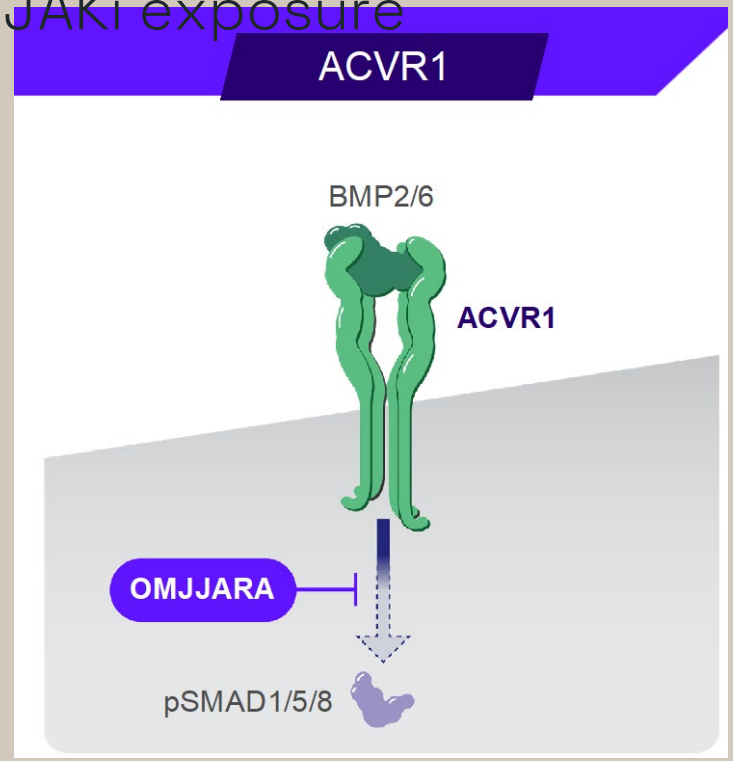


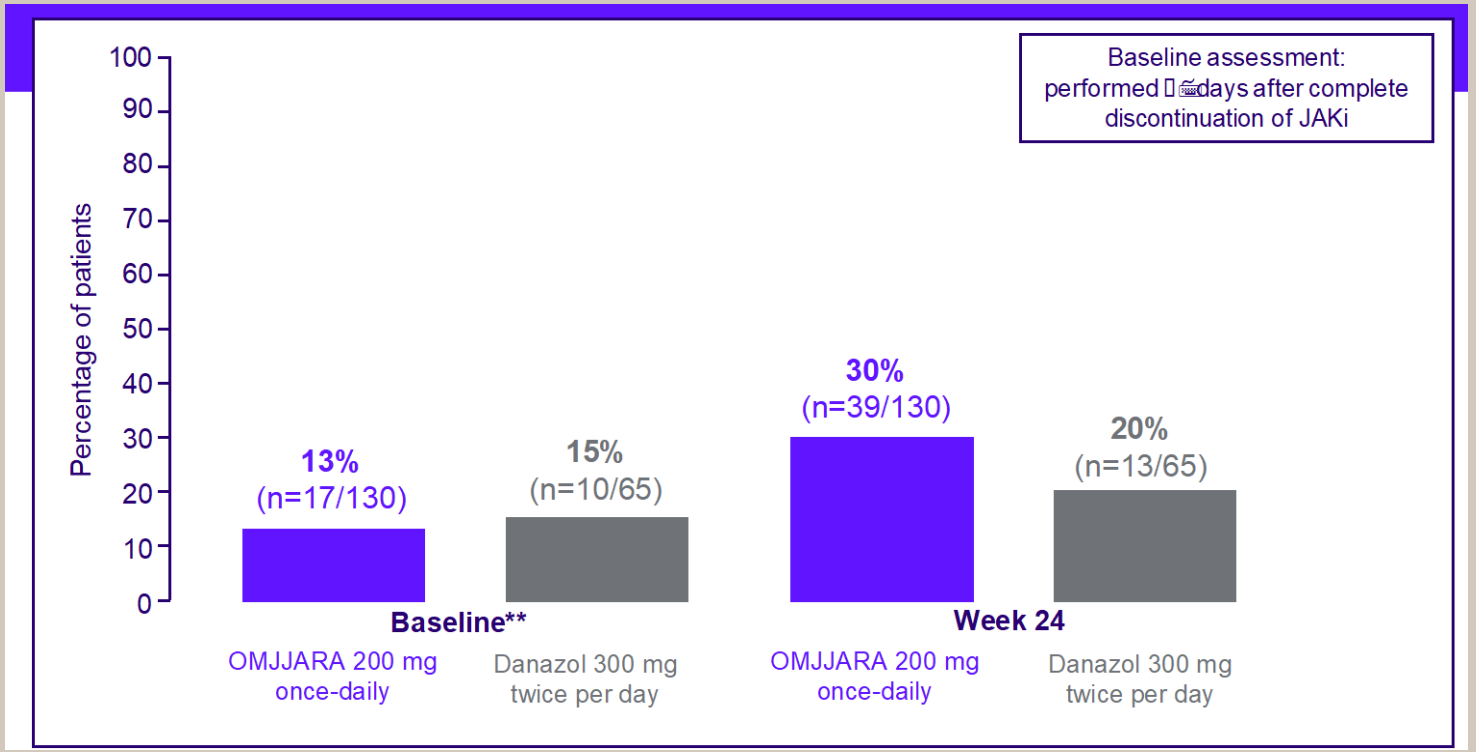


Mesa RA *et al. J Clin Oncol.* 2017;35(34):3844-3850

MOMENTUM Study

Phase 3 RCT momelotinib vs danazol in MF patients with anaemia and prior JAKi exposure





Inhibitor of ACVR1 within SMAD signalling pathway
Down regulates liver hepcidin expression resulting in increased iron availability and red blood cell production

Gerds AT *et al. Lancet Haematol.* 2023;10:e735-e746

Fedratinib

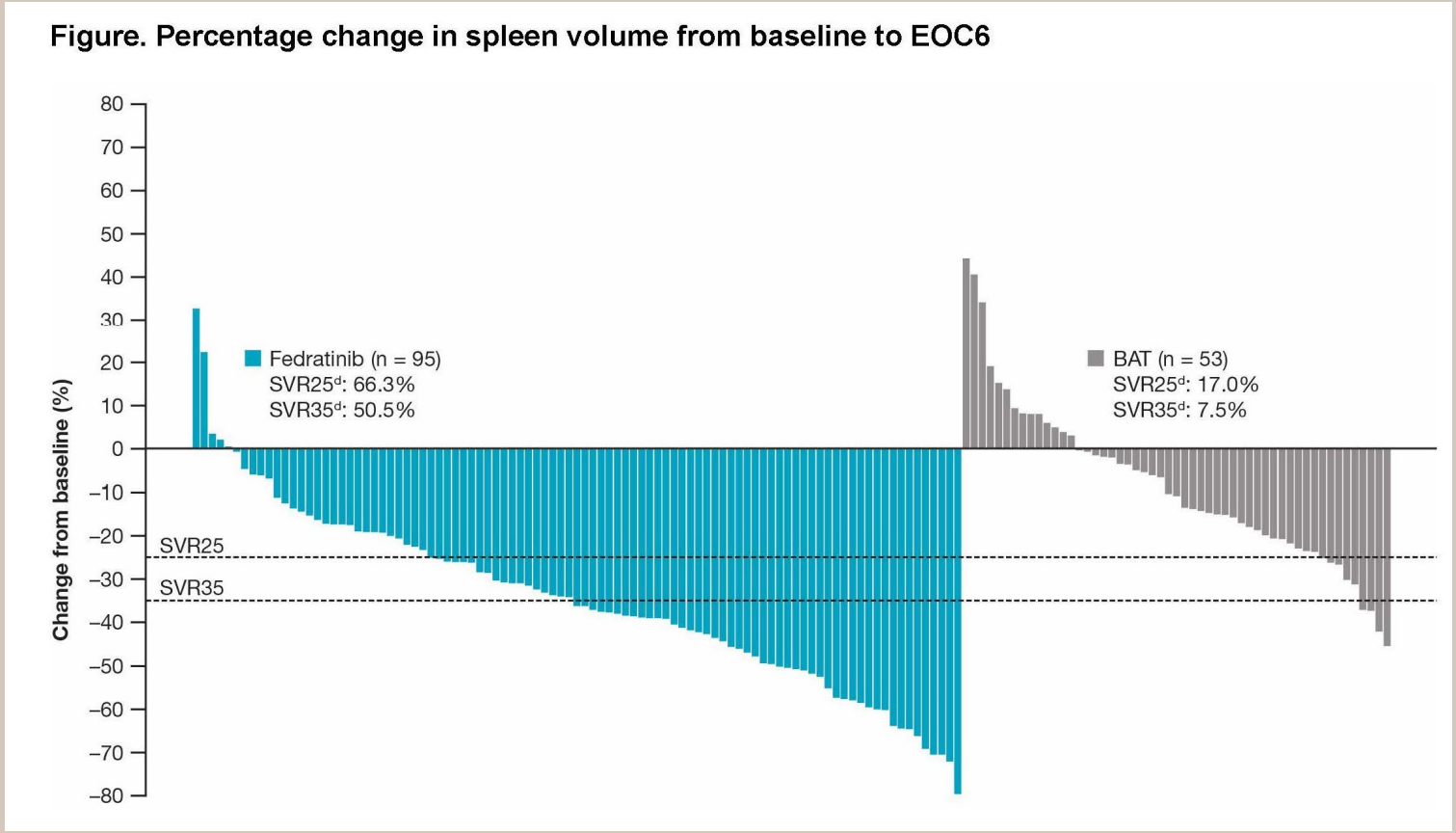
Selective JAK2 inhibitor

FREEDOM-2: IM2 or high-risk MF refractory or intolerant to rux

- 2:1 randomisation to FED vs BAT

SVR35 at end of cycle 6 in 36% of those receiving fedratinib versus 6% receiving BAT (p-value <0.0001).

Caution re. GI side effects



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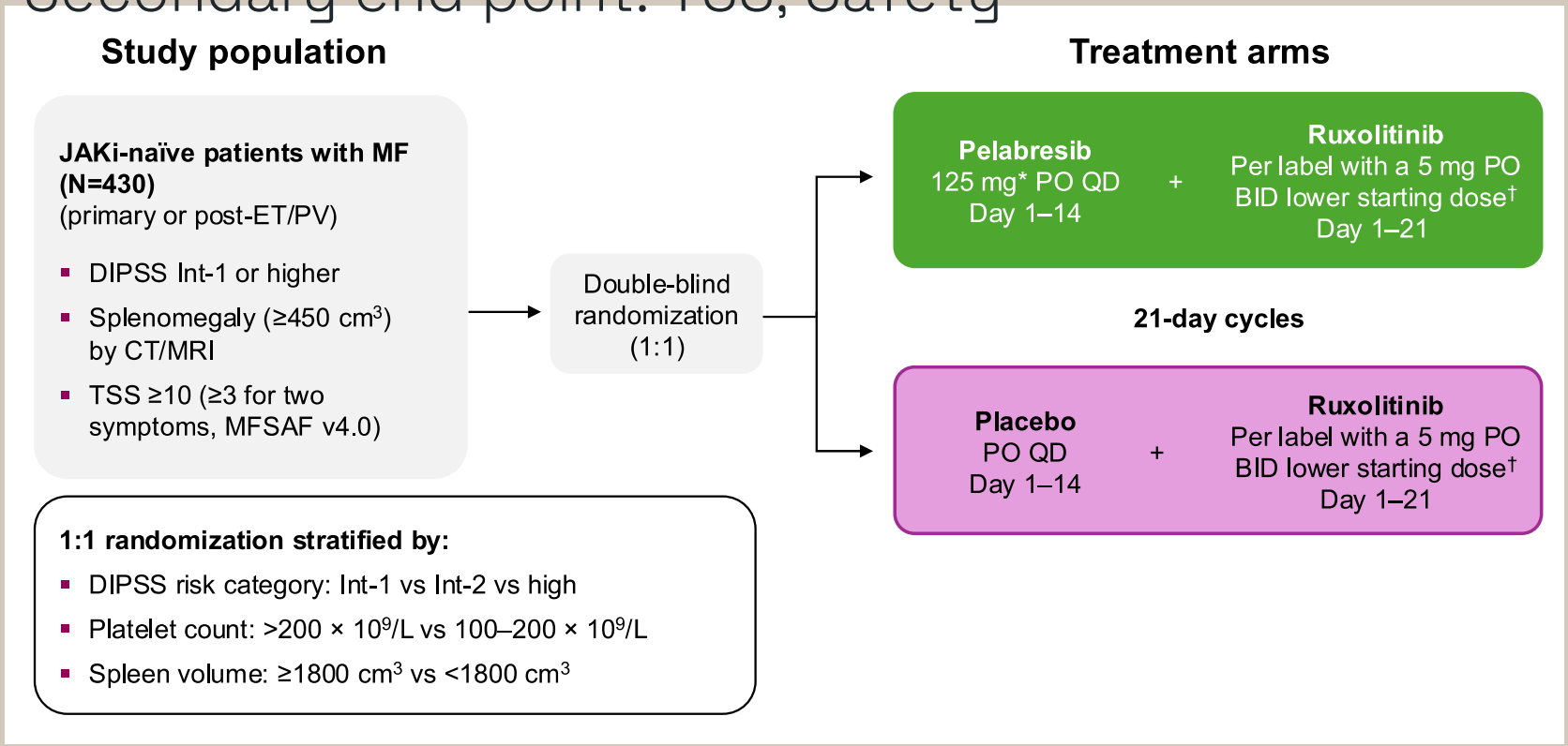
MANIFEST-2

Primary end point: SVR35 at week 24.

Secondary end point: TSS, Safety



SVR35 at week 24

Pelabresib+Rux + 65.9%

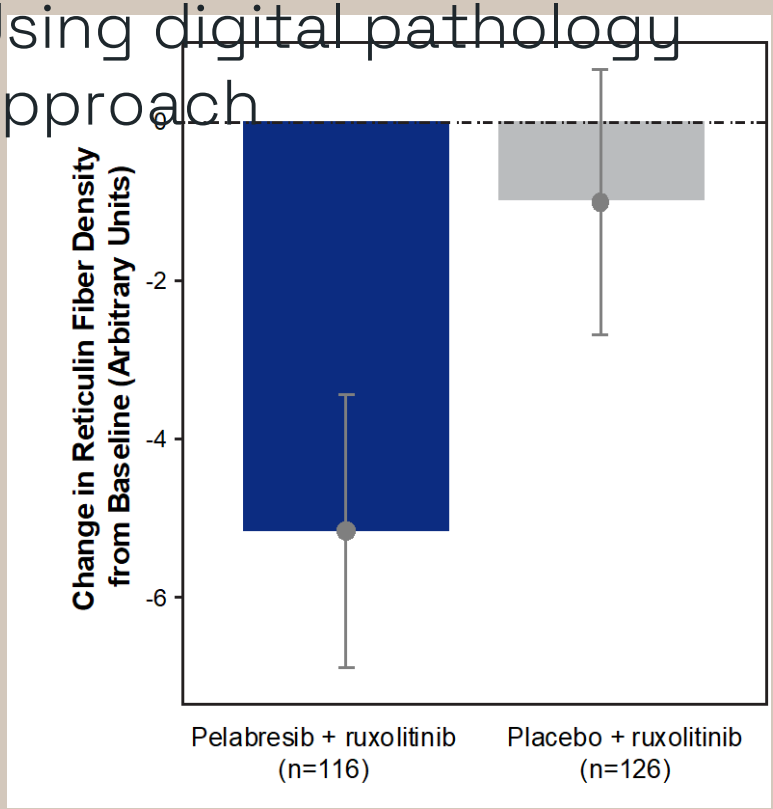
Placebo+Rux= 35.2%

P<0.001

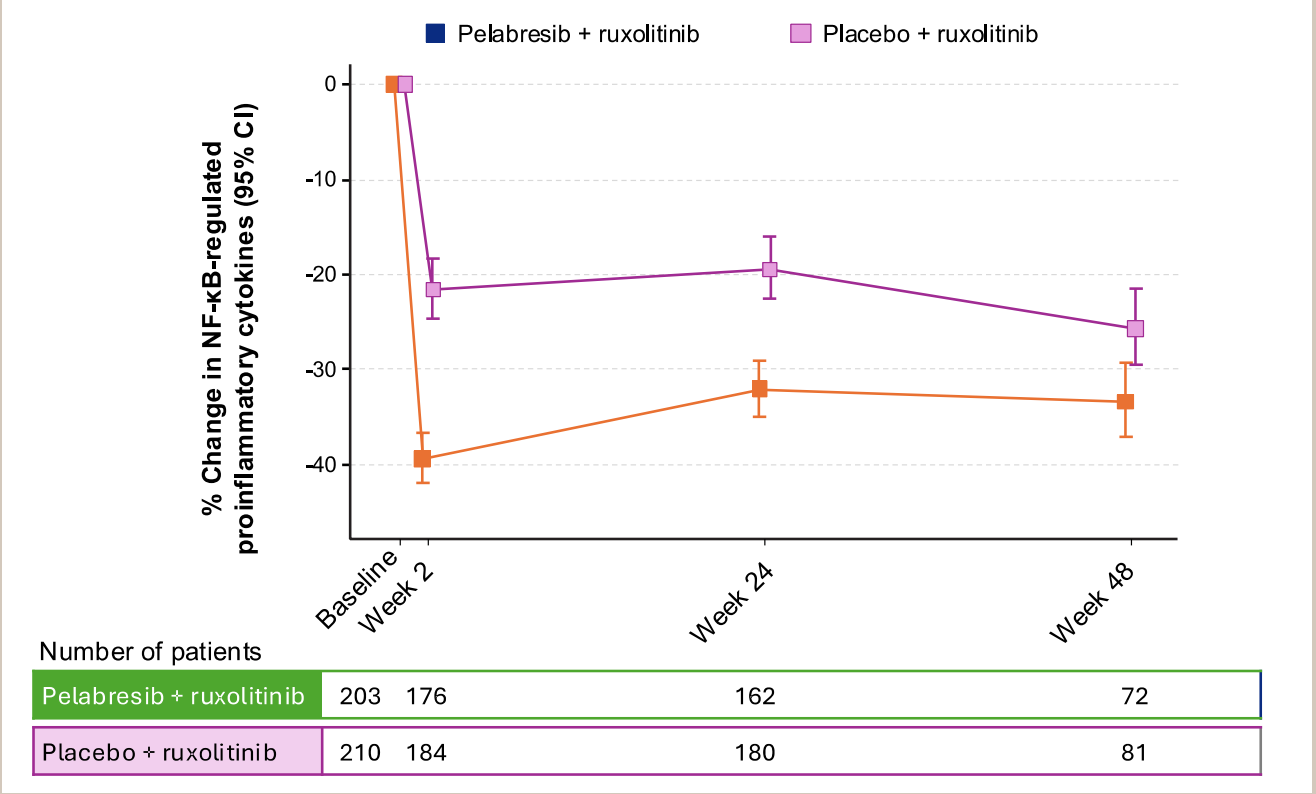
Rampal R, et al. Presented at ASH 2023 [Oral 628]

MANIFEST-2 – Disease Modifying Activity

Reticulin Fibre Density, week 24
Using digital pathology approach

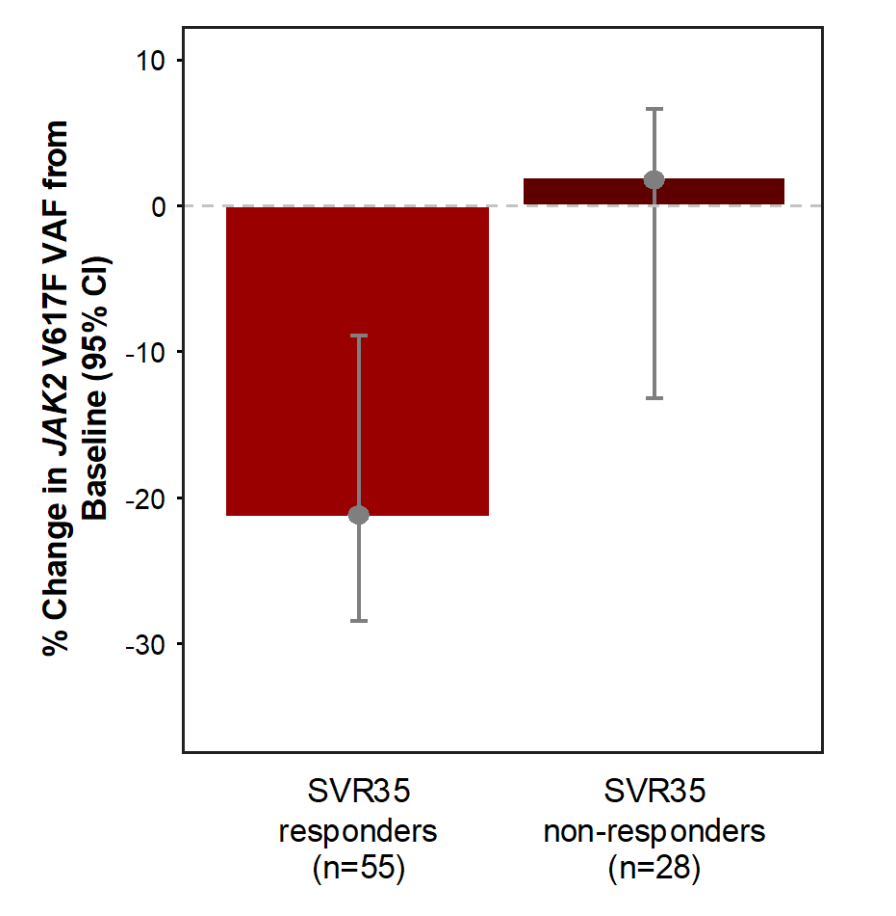


Proinflammatory Cytokines NFkB set: IL-6, IL-8 and TNFa



Rampal R, et al. Presented at ASH 2023 [Oral 628]

MANIFEST-2 – Molecular Response



- >50% reduction in 13% with pelabresib vs 8.1% with placebo
- Across all participants SVR35 correlates with JAK2V617F molecular response

	SVR35 Responders (N=55)	SVR35 Non-responders (N=28)	Nominal p-value mean difference
% Change in *JAK2* V617F VAF from baseline (mean, 95% CI)	-21.2 (-28.0, -9.1)	1.7 (-13.1, 6.3)	<0.001

Rampal R, et al. Presented at ASH 2023 [Oral 628]

TRANSFORM-1

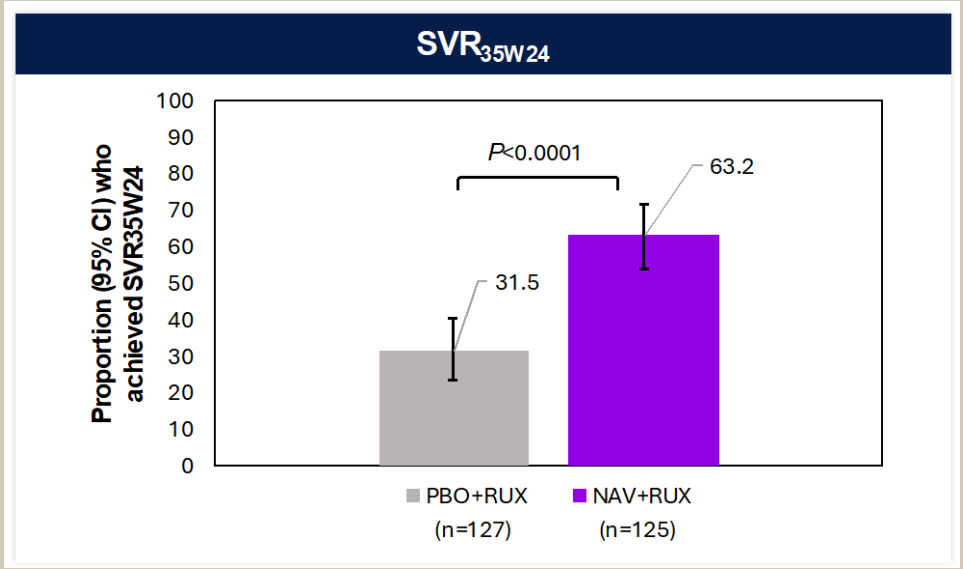
Assess BCL-2 inhibitor navitoclax in combination with ruxolitinib

JAK-inhibitor naïve patients
252 patients - 1:1 randomization
Navitoclax plus rux vs placebo plus rux

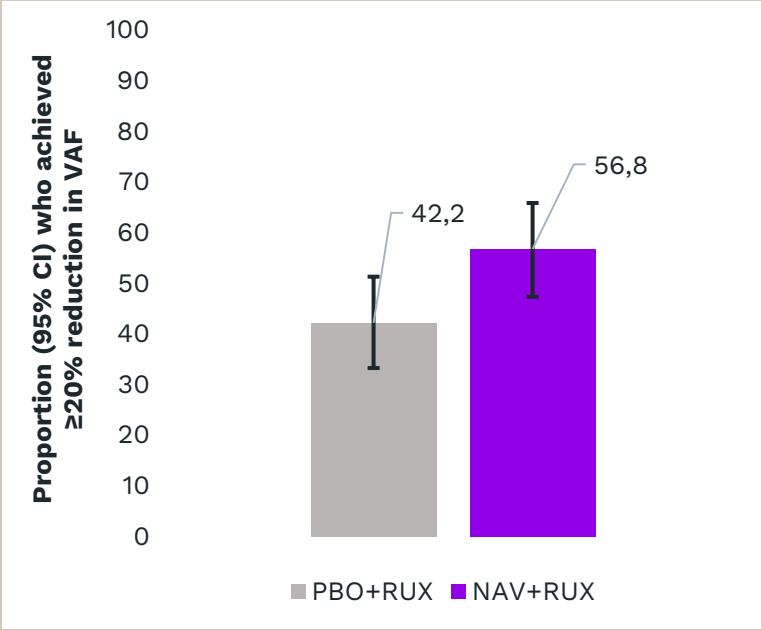
- IM2 or high-risk myelofibrosis with palpable splenomegaly

Primary end point 62.2% vs 31.5% (p<0.0001)

Pemmaraju et al., *Lancet Haematol. 2022;9(6):e434-e444*



Molecular Response



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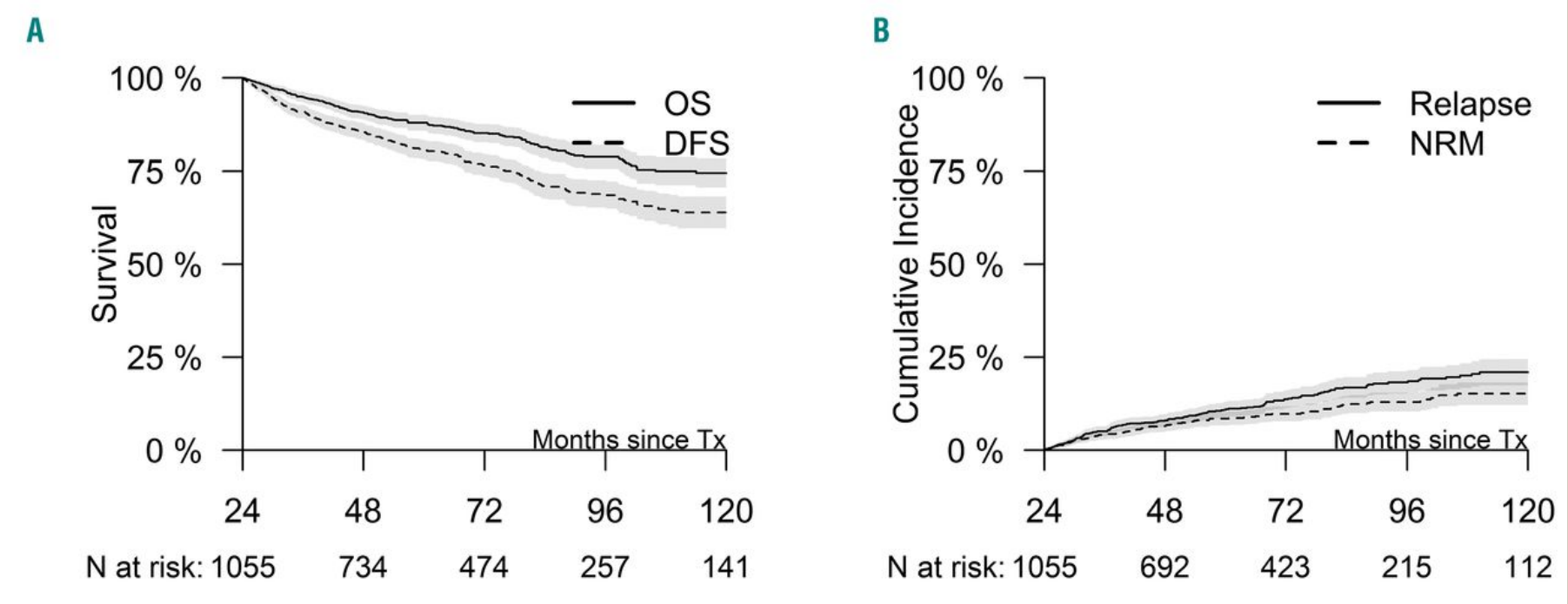
Allogeneic Stem Cell Transplantation

Remains only currently available durative option.

- Considered in those who are fit and have <5-year survival (Int-2 or High risk)

- Difficult – older patient population, splenomegaly, poor engraftment.



Robins et al. Haematologica 2019;104(9):1782-1788;

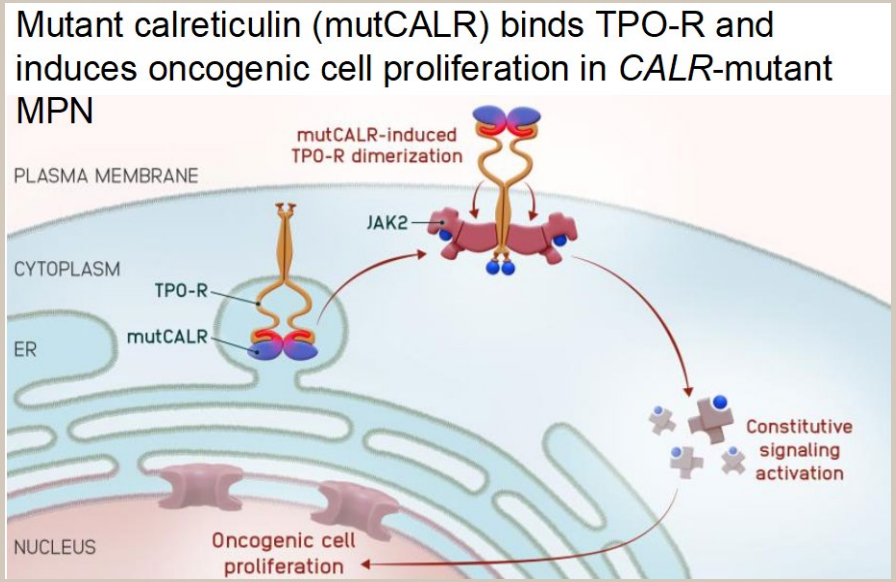
Future Directions

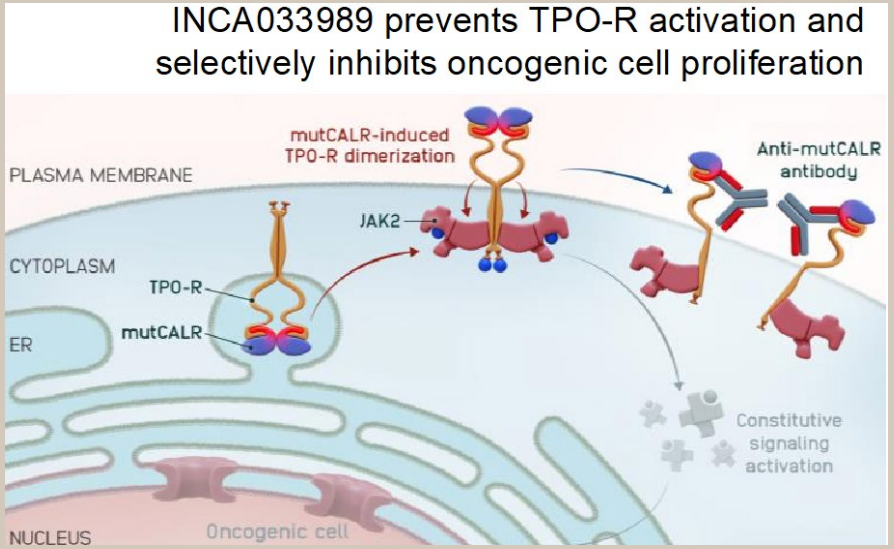
Additional JAKi combination studies

CALR directed immunotherapy

- Monoclonal antibody
- Vaccine studies
- Bispecific antibody
- CAR-T

Next generation JAKV617F specific inhibitors





Reis, Blood, https://doi.org/10.1182/blood.2024024373, 2024

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Questions

Thanks to GSTT MPN team and all patients