MPN Horizons

New Drugs - Myelofibrosis

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Disclosures

Consulting: Novartis, La Jolla, Samus, Sierra Oncology, Blueprint, Abbvie, BMS, Genentech, Roche, Geron

Research Support: Incyte, Celgene, CTI, Promedior, Genentech, Abbvie, Imago

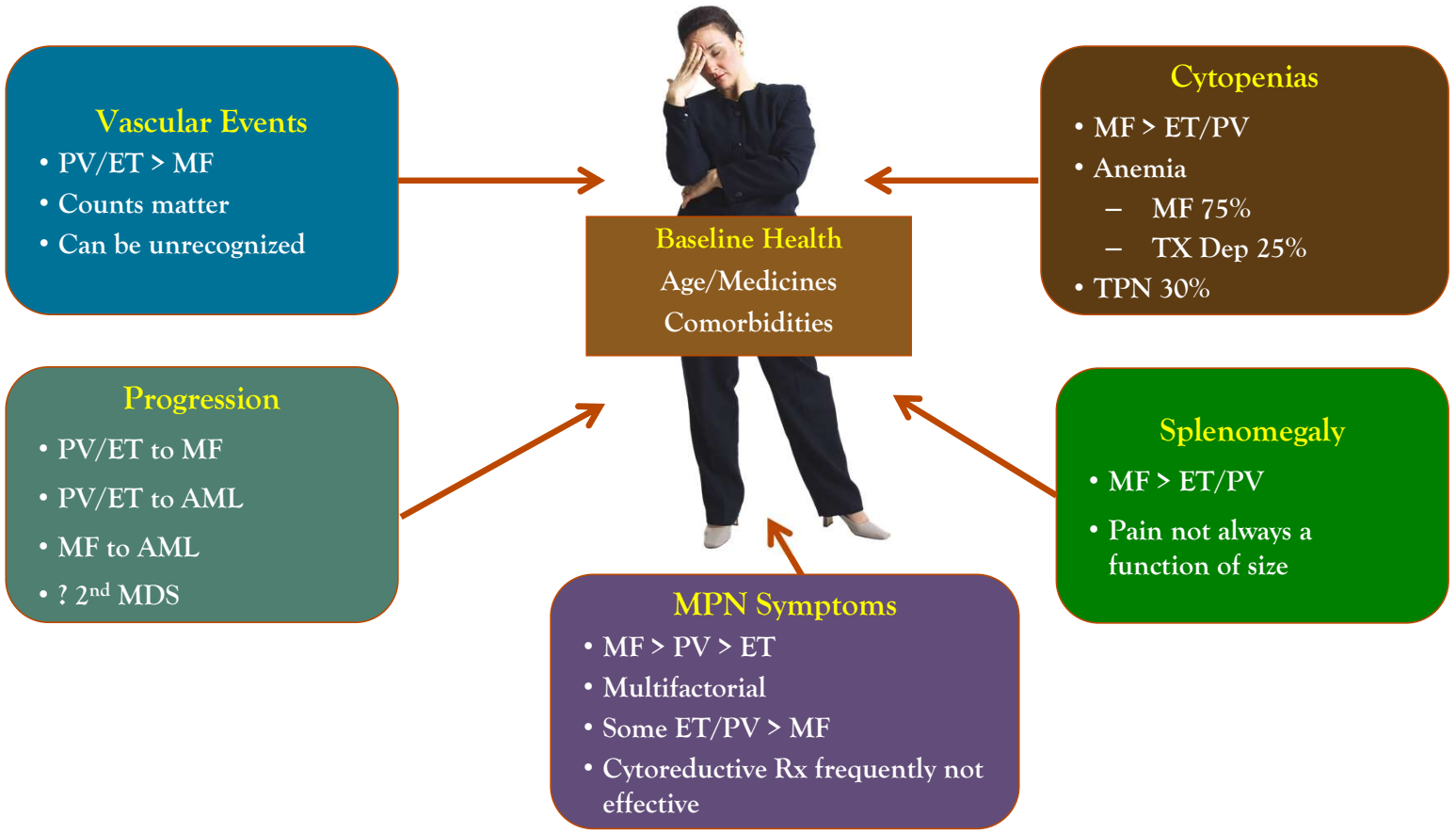
Off Label Use: Hydroxyurea, PEG Interferon, ruxolitinib

New Drugs - MF

- Burden of Having MF
- JAK Inhibitors
- New Drugs Front Line
- New Drugs Second Line
- Future State

Assessing MPN Burden

WHO Diagnosis Does Not Tell Whole Story



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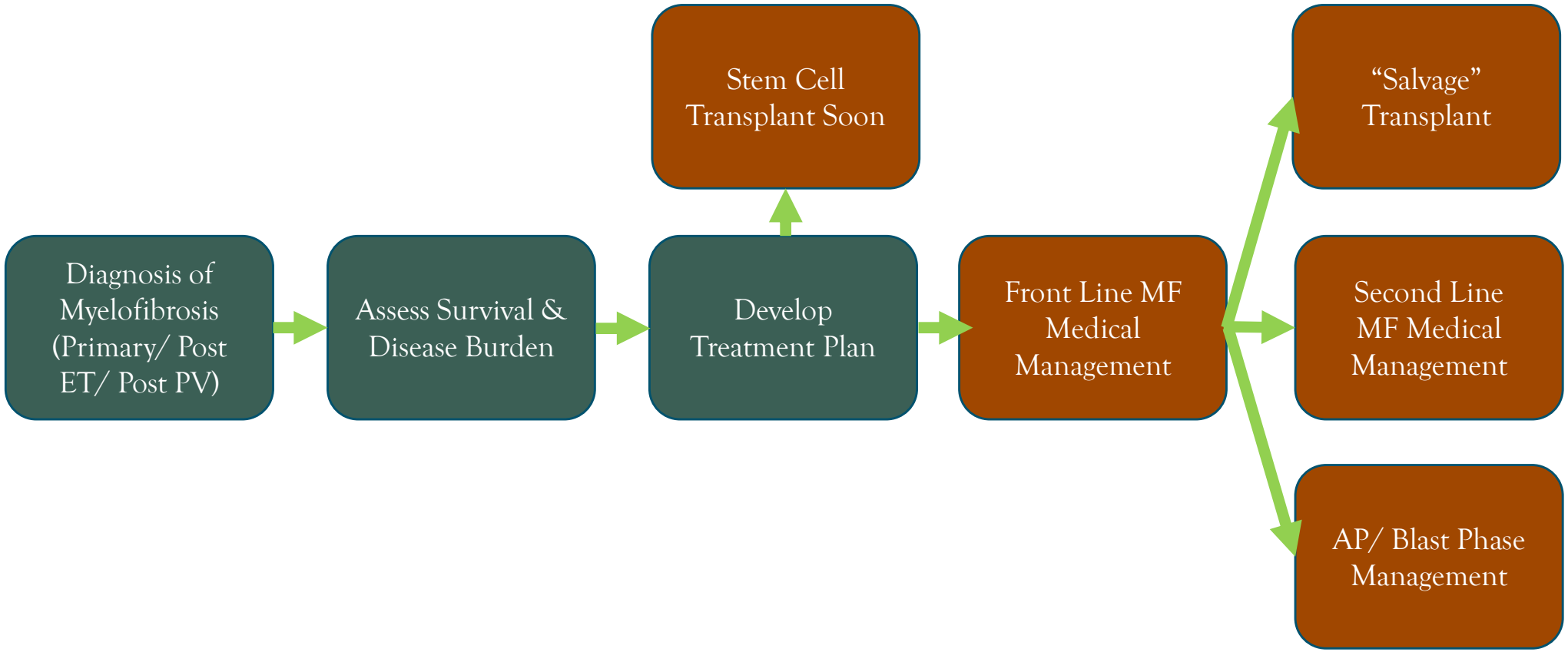
Management of Myelofibrosis 2021



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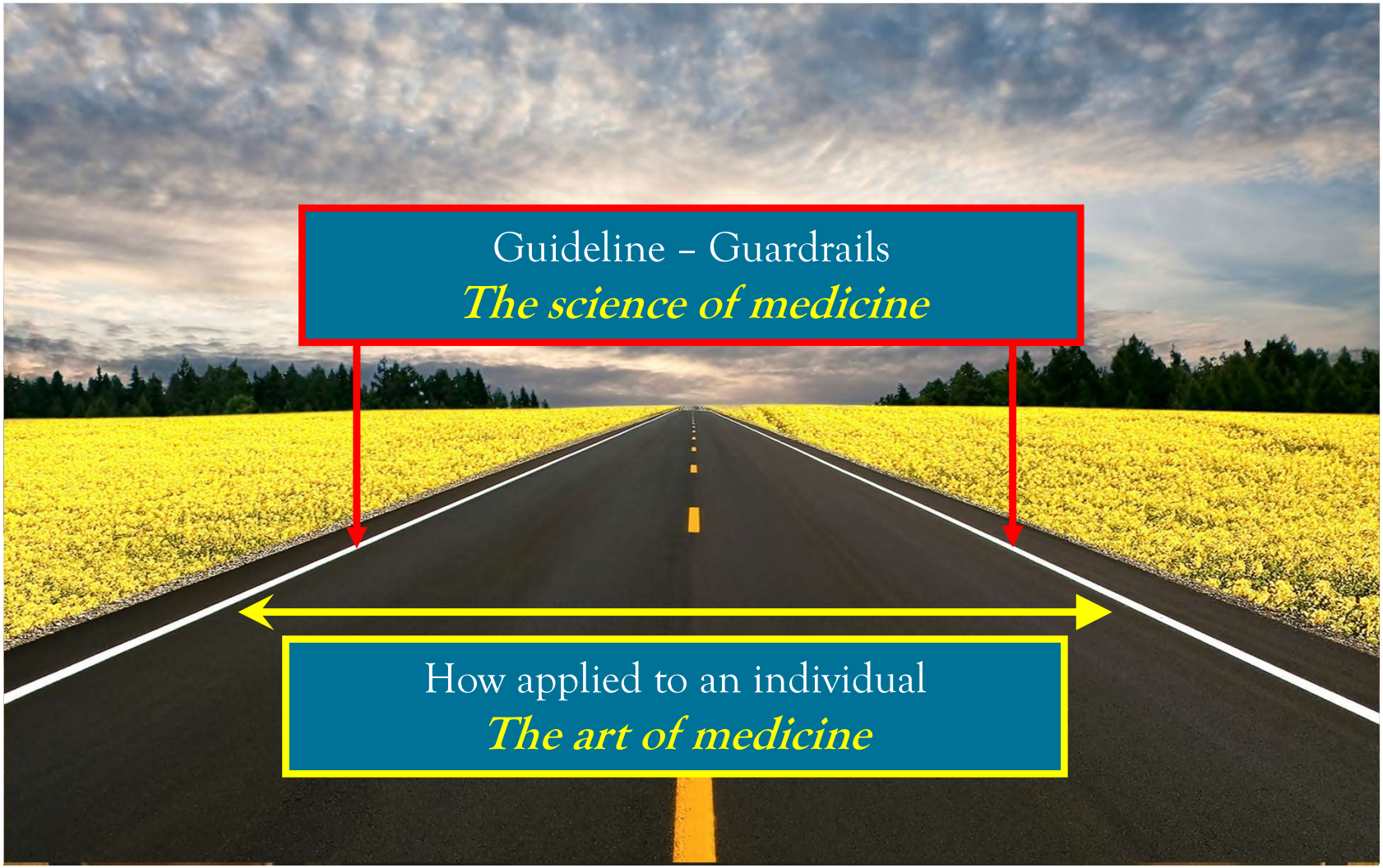
What is a treatment guideline?



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NCCN Guidelines Version 1.2021
Myelofibrosis
NCCN Evidence Blocks™

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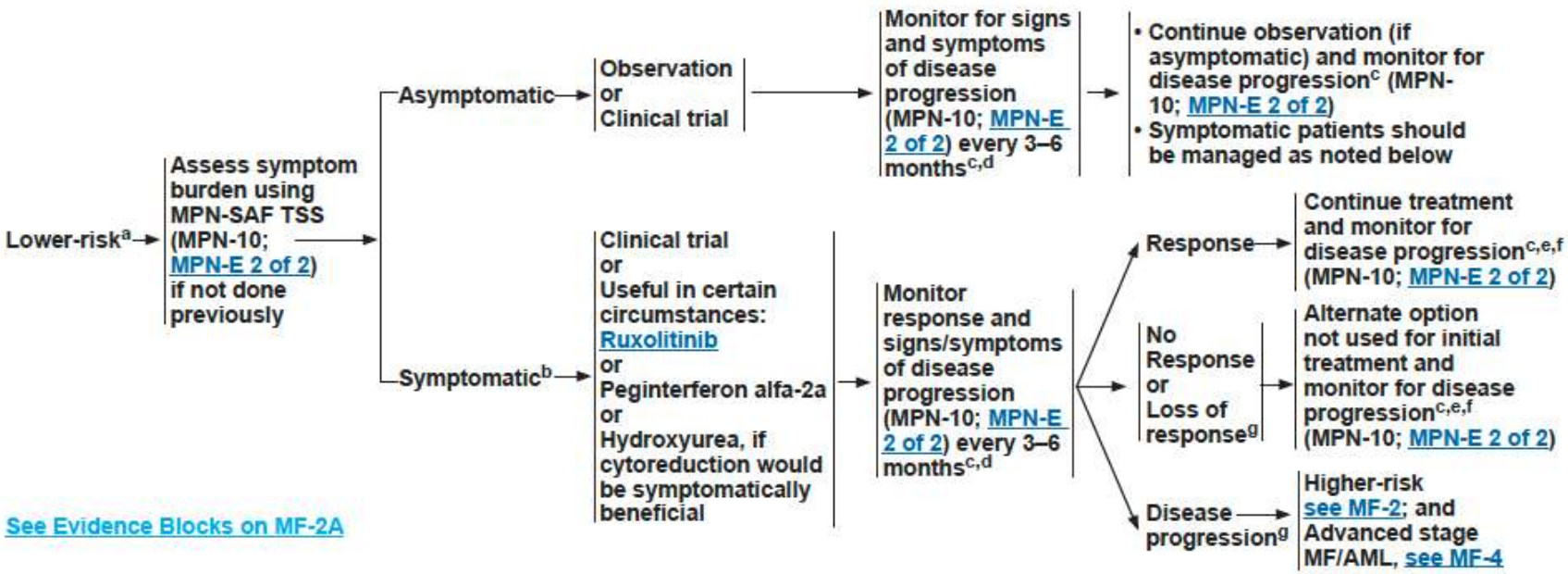
TREATMENT FOR LOWER-RISK MYELOFIBROSIS



See Evidence Blocks on MF-2A

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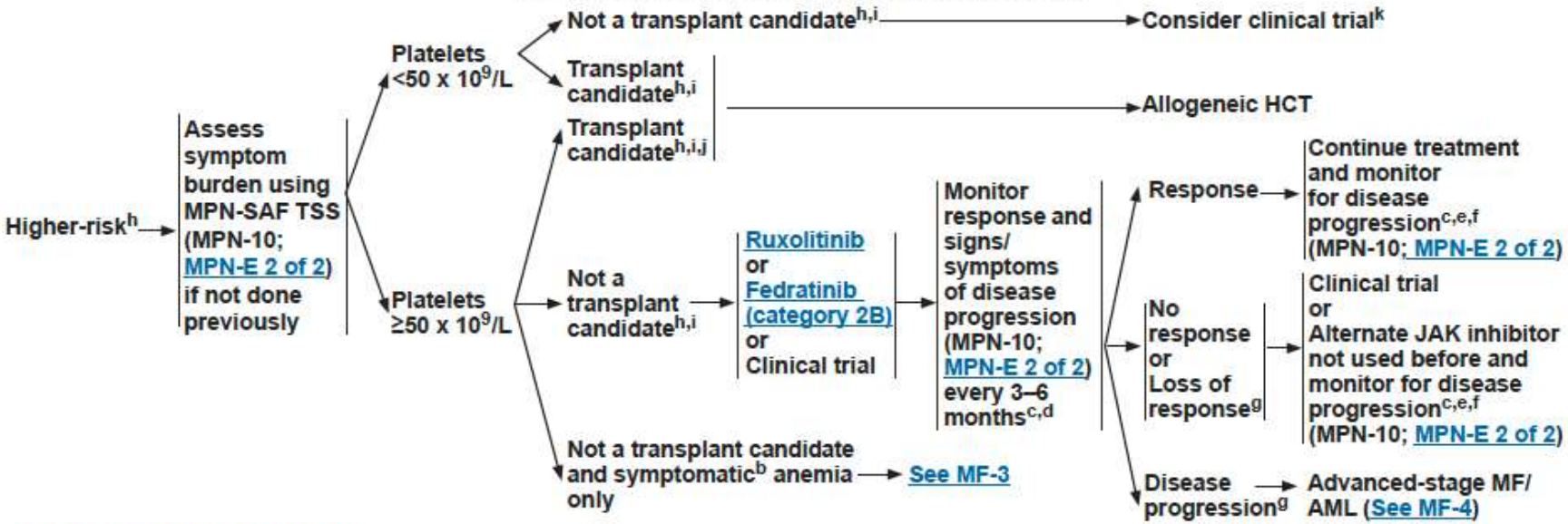
TREATMENT FOR HIGHER-RISK MYELOFIBROSIS



See Evidence Blocks on MF-2A

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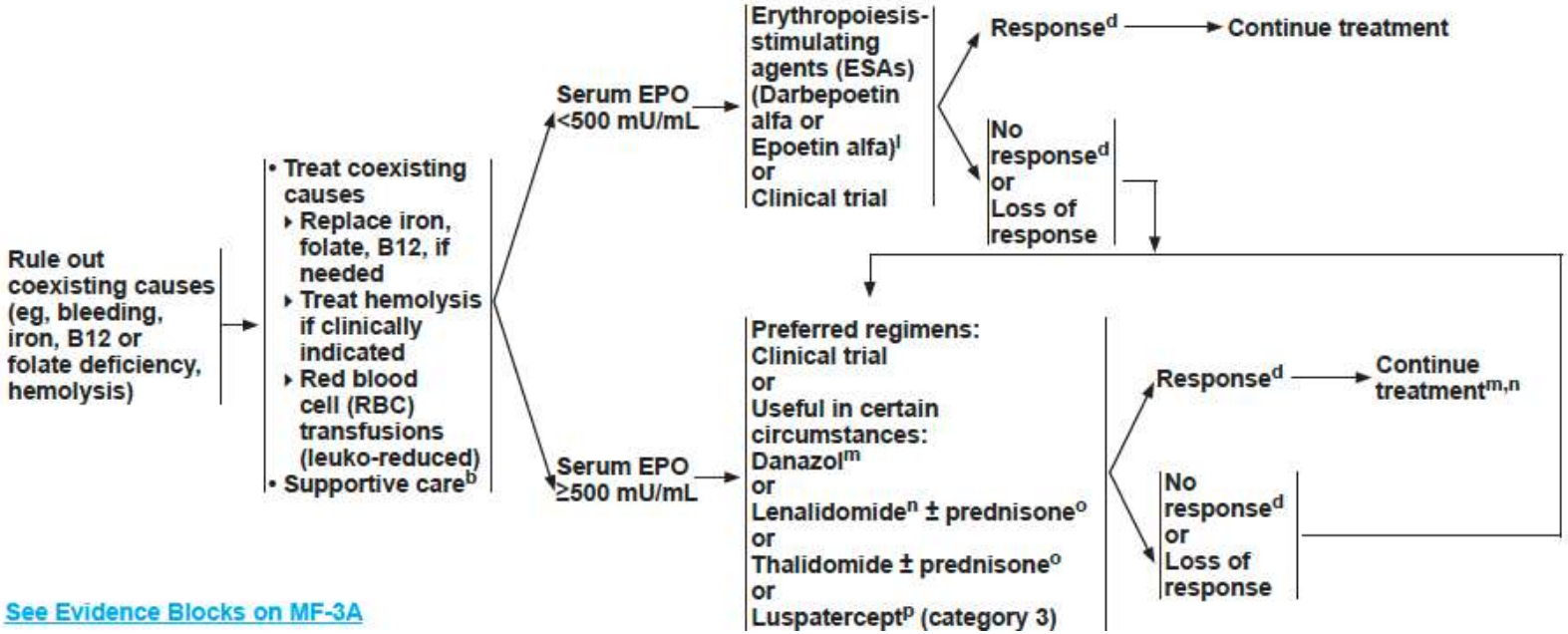
MANAGEMENT OF MF-ASSOCIATED ANEMIA[j]



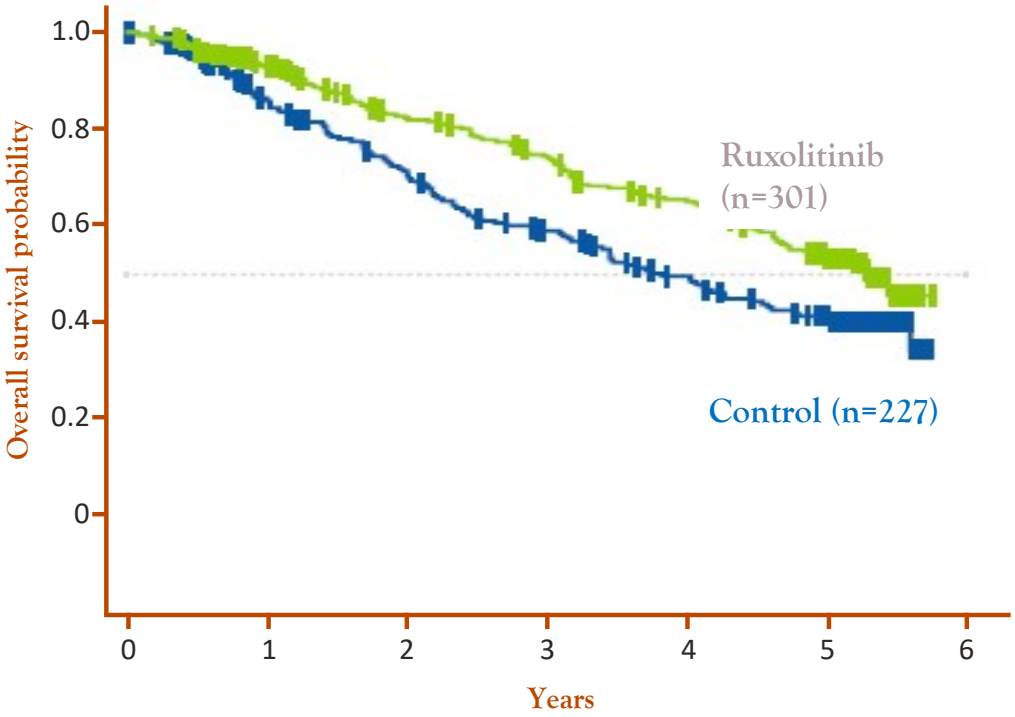
See Evidence Blocks on MF-3A

New Drugs - MF

- Burden of Having MF
- JAK Inhibitors
- New Drugs Front Line
- New Drugs Second Line
- Future State

Results from the COMFORT studies demonstrated improvement of survival outcomes in patients treated with ruxolitinib

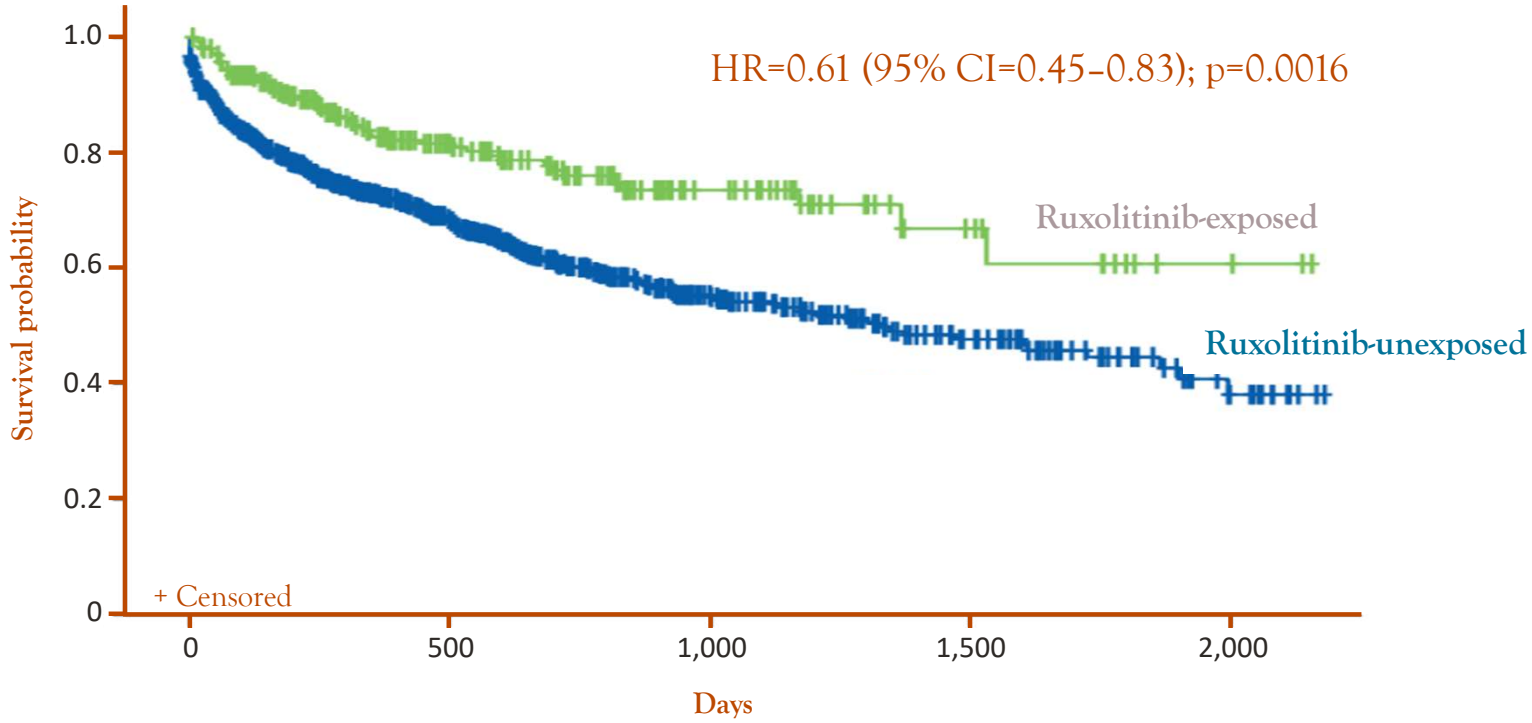
OS from COMFORT I and COMFORT II 5-year pooled exploratory analysis (N=528)



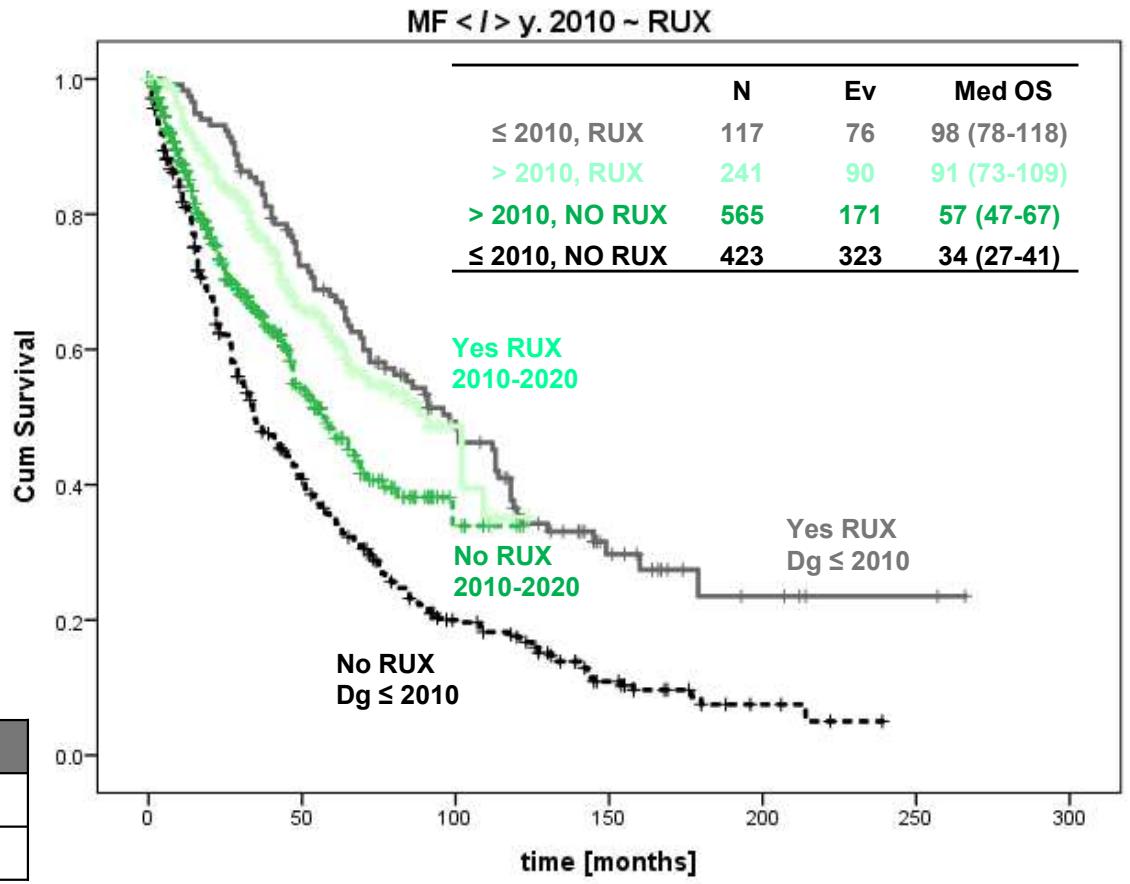
	Ruxolitinib (n=301)	Control (n=227)
Deaths, n (%)	128 (42.5)	117 (51.5)
Median OS, years (95% CI)	5.3 (4.7–NE)	3.8 (3.2–4.6)
HR (95% CI); p-value	0.70 (0.54–0.91); p=0.0065	

Real-world evidence demonstrated survival benefits of ruxolitinib in elderly patients with MF

Overall survival in patients with newly diagnosed intermediate- or high-risk MF (N=1399)



Results: OS ~ Ruxolitinib



OS without and with rux ~ years 2010
≤ y. 2010, p < 0.001, HR 0.46, 95% CI 0.35-0.59
> y. 2010, p = 0.001, HR 0.66, 95% CI 0.51-0.85

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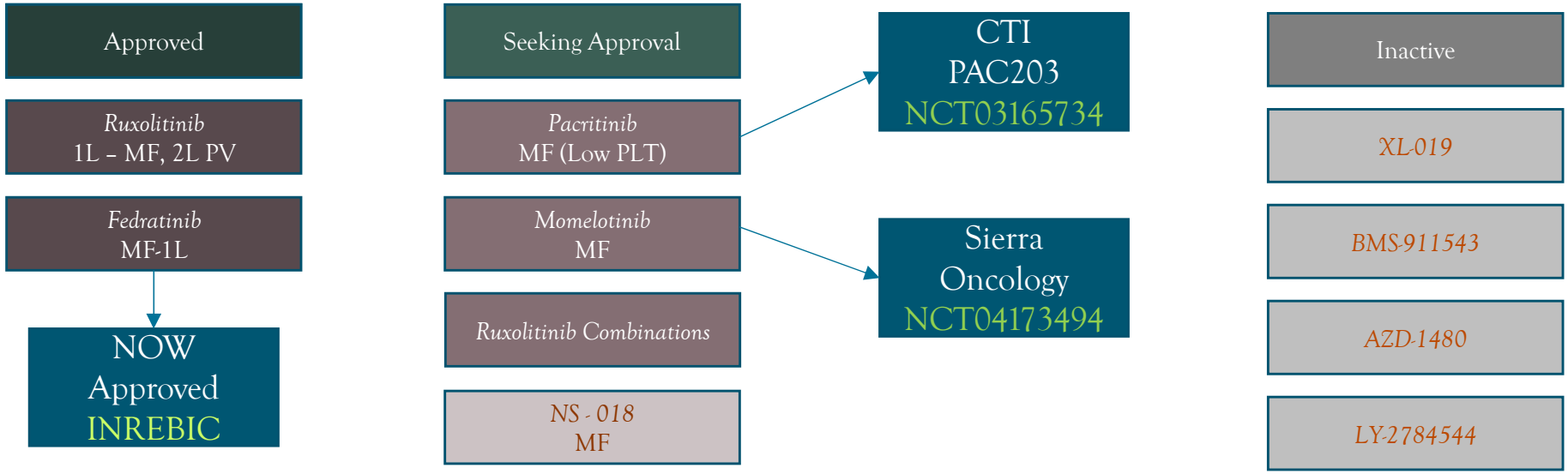
Masarova et. al. ASH 2020

JAK Inhibitor Landscape 2021



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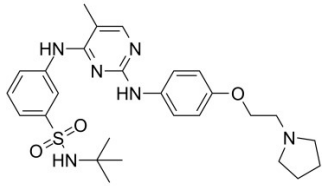
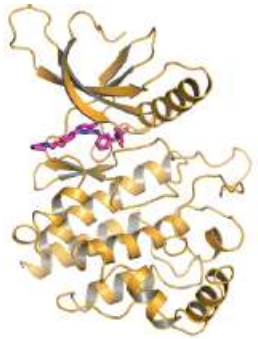
Fedratinib

INREBIC® (Fedratinib)

- Oral, JAK2-selective inhibitor recently approved in the US for treatment of intermediate-2 or high-risk primary or secondary (post-PV or post-ET) MF with **platelet counts ≥50 × 10^9/L**[3]
- Fedratinib has higher inhibitory activity for JAK2 over JAK1, JAK3, and TYK2[4]
- Fedratinib was investigated for treatment of MF in JAK-inhibitor-naïve patients in the phase III JAKARTA trial, and in patients previously treated with RUX in the phase II JAKARTA2 trial
- JAKARTA and JAKARTA2 allowed enrollment of patients with platelet counts of ≥50 × 10^9/L at study entry



FEDRATINIB



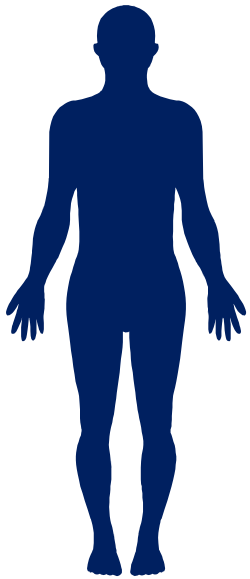
JAK2 KINASE DOMAIN – Fedratinib Complex[7]

1. Jakafi (ruxolitinib) prescribing information. Incyte Corporation; 05/2019. 2. Center for Drug Evaluation and Research. Clinical Pharmacology Genomics Group Review; 2011.
3. INREBIC® (fedratinib) prescribing information. Celgene Corporation; 08/2019. 4. Wernig et al. *Cancer Cell.* 2008;13:311–20. 5. Pardanani et al. *JAMA Oncol.* 2015;1(5):643–51.
6. Harrison et al. *Lancet Haematol.* 2017;4:e317–24. 7. Hantschel O. *ACS Chem Biol.* 2015;10(1):234-45.
BL, baseline ET, essential thrombocythemia; JAK, Janus kinase; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera; RUX, ruxolitinib.

Fedratinib in Myelofibrosis: JAKARTA and JAKARTA-2 Trials

Phase 3 JAKARTA Trial

Fedratinib vs placebo in patients with Int-2/high-risk MF



N = 289

	Fedratinib 400 mg	Fedratinib 500 mg
Spleen volume reduction ≥ 35%	37%	40%
Symptom burden reduction ≥ 50%	40%	34%
Discontinuation due to AEs	14%	25%

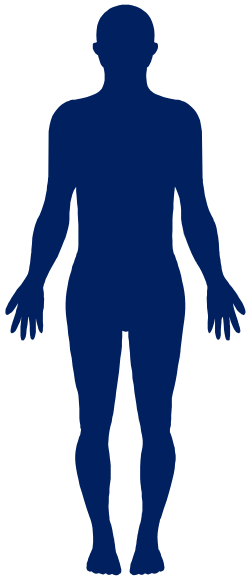
AE = Adverse Event; Int-2 = Intermediate-2

Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643–651; Harrison CN, et al. *Lancet Haematol*. 2017;4(7):317–324; Harrison CN, et al. ASCO 2019. Abstract 7057.

Fedratinib in Myelofibrosis: JAKARTA and JAKARTA-2 Trials

Phase 2 JAKARTA-2 Trial

Fedratinib vs placebo in patients with Int-2/high-risk MF resistant or intolerant to ruxolitinib



N = 97
*N = 79

	Primary analysis	Reanalysis (2019)*
Spleen volume reduction ≥ 35%	55%	30%
Symptom burden reduction ≥ 50%		27%
Discontinuation due to AEs	11.0%	

*More stringent criteria for relapse, refractory, and intolerance to ruxolitinib

Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643–651; Harrison CN, et al. *Lancet Haematol*. 2017;4(7):317–324; Harrison CN, et al. ASCO 2019. Abstract 7057.

EUROPEAN HEMATOLOGY ASSOCIATION

Overall and progression-free survival in patients treated with fedratinib as first-line myelofibrosis therapy and after prior ruxolitinib: results from the JAKARTA and JAKARTA2 trials

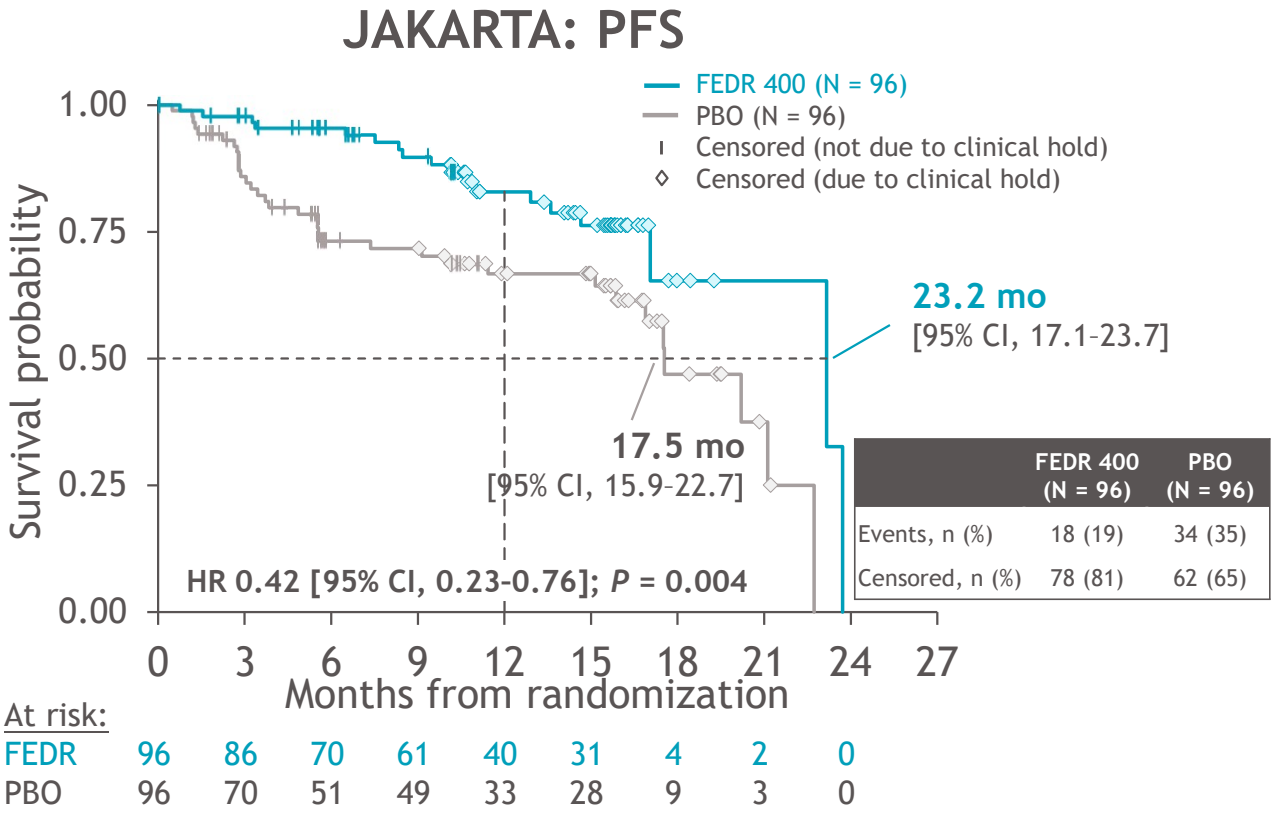
Claire Harrison,[1] Jean-Jacques Kiladjian,[2] Srdan Verstovsek,[3] Alessandro Vannucchi,[4] Ruben Mesa,[5] Andreas Reiter,[6] Jun Zhang,[7] Shelonitda Rose,[7] and John Mascarenhas[8]

[1]Guy's and St Thomas' Hospital, London, United Kingdom; [2]Hôpital Saint-Louis and Université de Paris, Paris, France; [3]The University of Texas MD Anderson Cancer Center, Houston, United States; [4]AOU Careggi, University of Florence, Florence, Italy; [5]Mays Cancer Center at UT Health San Antonio MD Anderson, San Antonio, United States; [6]Universitätsklinikum Mannheim, Mannheim, Germany; [7]Bristol Myers Squibb, Princeton, United States; [8]Icahn School of Medicine at Mount Sinai, New York, United States

Presentation S203

JAKARTA: Progression-free survival

- **FEDR 400 significantly reduced the risk of disease progression vs. PBO (*P* = 0.004)**
  - Median PFS was 5.7 months longer in the FEDR 400 arm vs. PBO: 23.2 vs. 17.5 mo, respectively
  - 1-year PFS: FEDR 400 83%, PBO 67%
- **80 pts (42%) were still being followed for PFS at the time of clinical hold**
  - Median follow-up: FEDR 400, 10.6 mo; PBO, 9.1 mo
- AML transformation was reported in 3 pts (3%) in the FEDR 400 arm and 2 pts (2%) in the PBO arm[a]



	FEDR 400 (N = 96)	PBO (N = 96)
Events, n (%)	18 (19)	34 (35)
Censored, n (%)	78 (81)	62 (65)

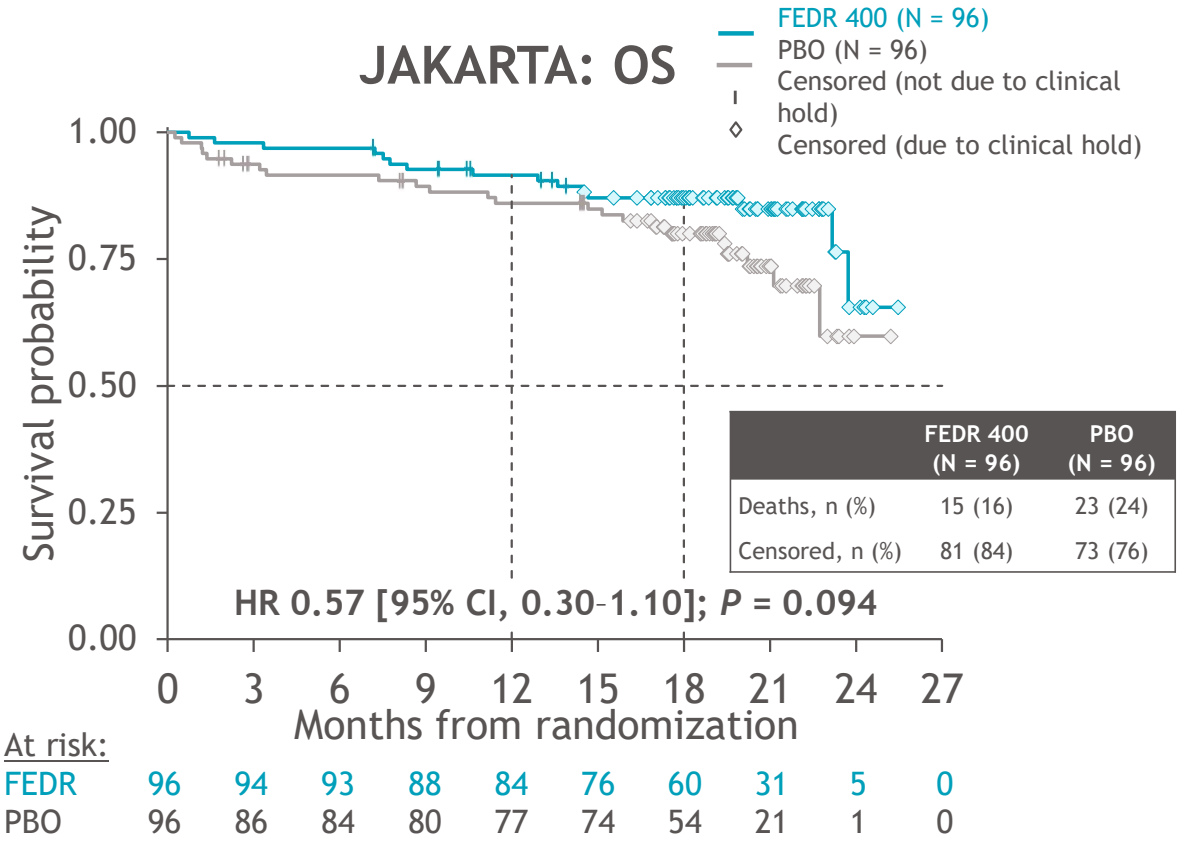
[a]AML transformation was based on adverse event reporting, including the preferred terms of "*Acute myeloid leukemia*", "*Acute leukemia*", and "*Transformation to acute myeloid leukemia*".

P value from log-rank test.

AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio; FEDR, fedratinib; mo, months; PBO, placebo; PFS, progression-free survival; pts, patients.

JAKARTA: Overall survival (ITT)

- **Median OS was not reached (NR) in the FEDR 400 [95%CI, 23.7 mo - NR] or PBO [22.7 - NR] arm**
  - 1-year OS rates: FEDR 400 mg, 92%; PBO, 86%
  - 18-mo OS rates: FEDR 400 mg, 87%; PBO, 80%
- ITT analysis; 74% of PBO-randomized pts crossed-over to FEDR after EOC6
- **139 pts (72%) were censored for OS at the time of clinical hold**
  - Median follow-up: FEDR 400 mg, 19.3 mo; PBO, 18.8 mo



	FEDR 400 (N = 96)	PBO (N = 96)
Deaths, n (%)	15 (16)	23 (24)
Censored, n (%)	81 (84)	73 (76)

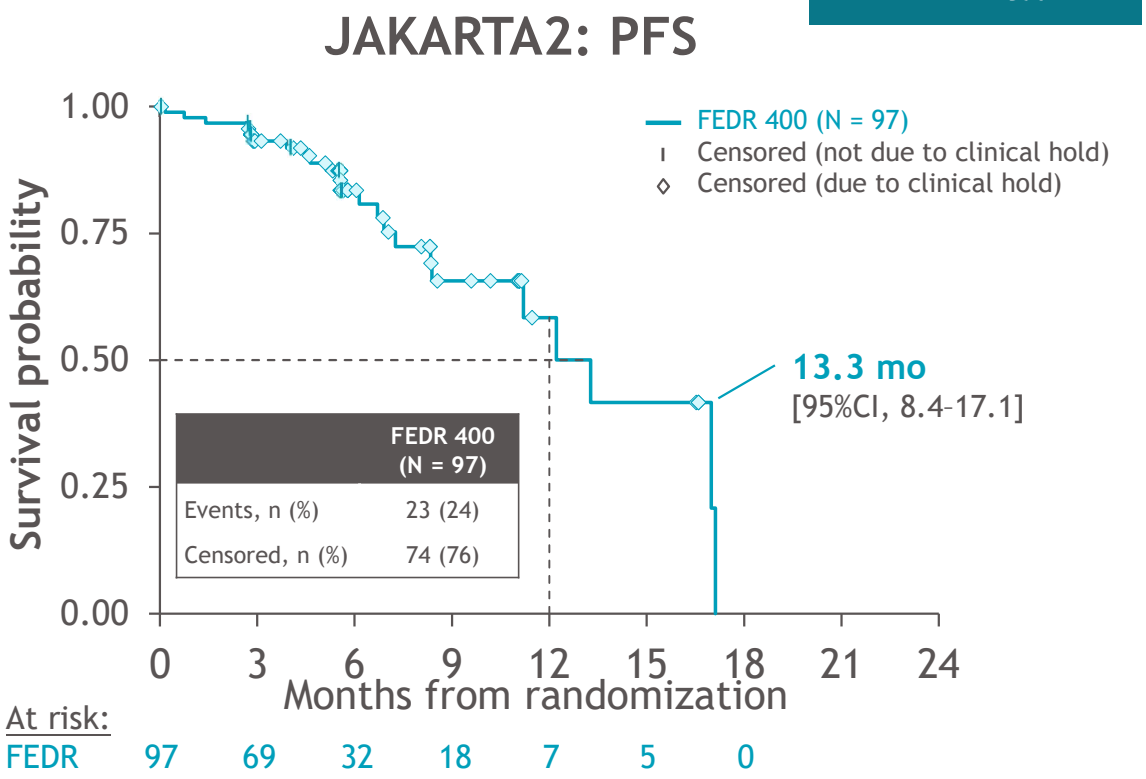
P value from log-rank test.

CI, confidence interval; HR, hazard ratio; FEDR, fedratinib; mo, months; NR, not reached; OS, overall survival; PBO, placebo; pts, patients.

JAKARTA2: Progression-free survival

Note: Single Arm Trial

- **Median PFS was 13.3 mo**
  - 1-year PFS rate was 59%
- **62 pts (64%) were still being followed for PFS at the time of clinical hold**
  - Median follow-up: 5.6 mo
- 2 pts (2%) experienced transformation to AML during the JAKARTA2 Tx period[a]

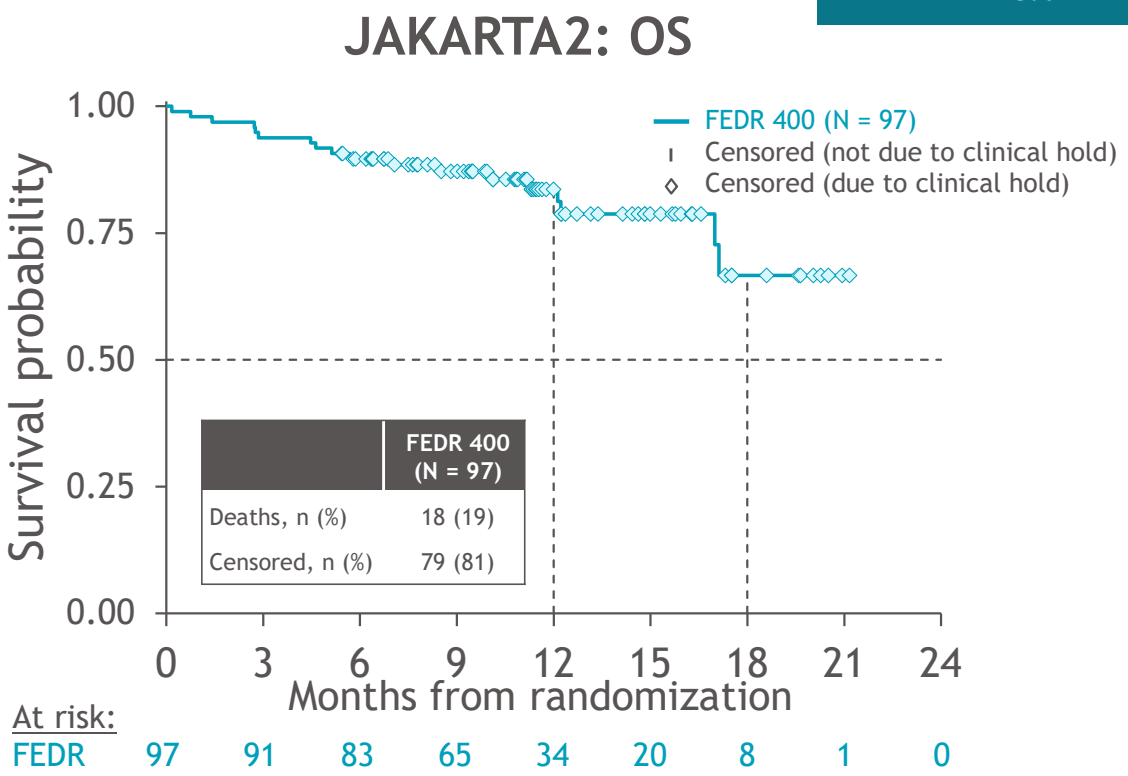


[a]AML transformation was based on adverse event reporting, including the preferred terms of "*Acute myeloid leukemia*", "*Acute leukemia*", and "*Transformation to acute myeloid leukemia*".
AML, acute myeloid leukemia; FEDR, fedratinib; mo, months; PFS, progression-free survival; pts, patients; Tx, treatment.

JAKARTA2: Overall survival

Note: Single Arm Trial

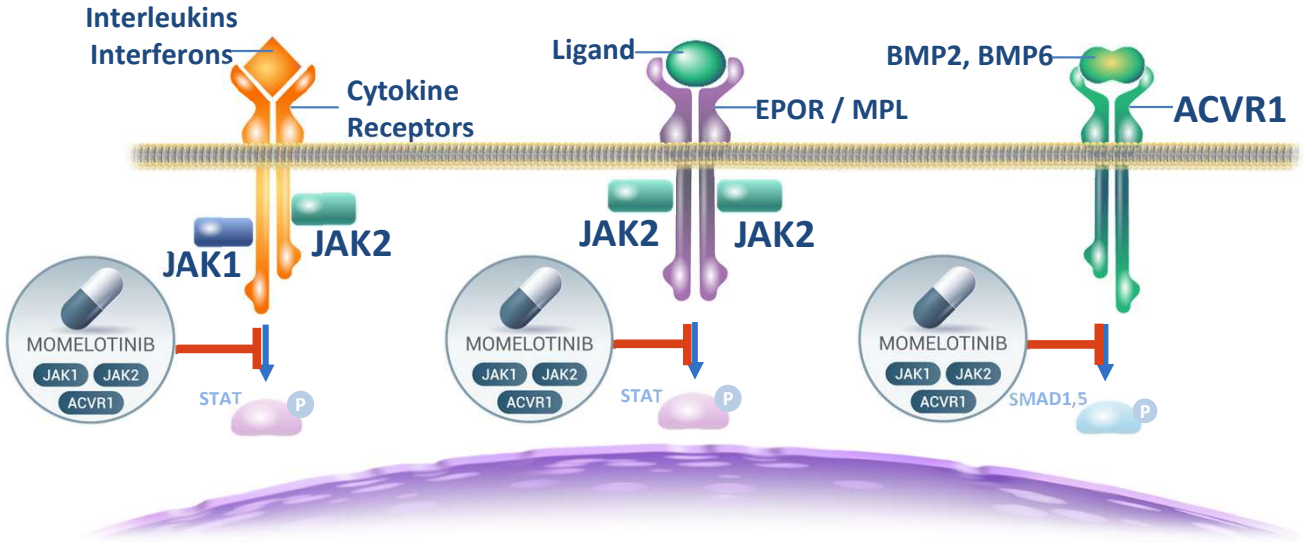
- **Median OS was NR [95%CI, 17.1 – NR]**
  - 1-year and 18-mo OS rates were 84% and 67%, respectively
- **79 pts (81%) were censored for OS at the time of clinical hold**
  - Median follow-up: 10.8 mo



FEDR, fedratinib; mo, months; NR, not reached; OS, overall survival; PBO, placebo; pts, patients.

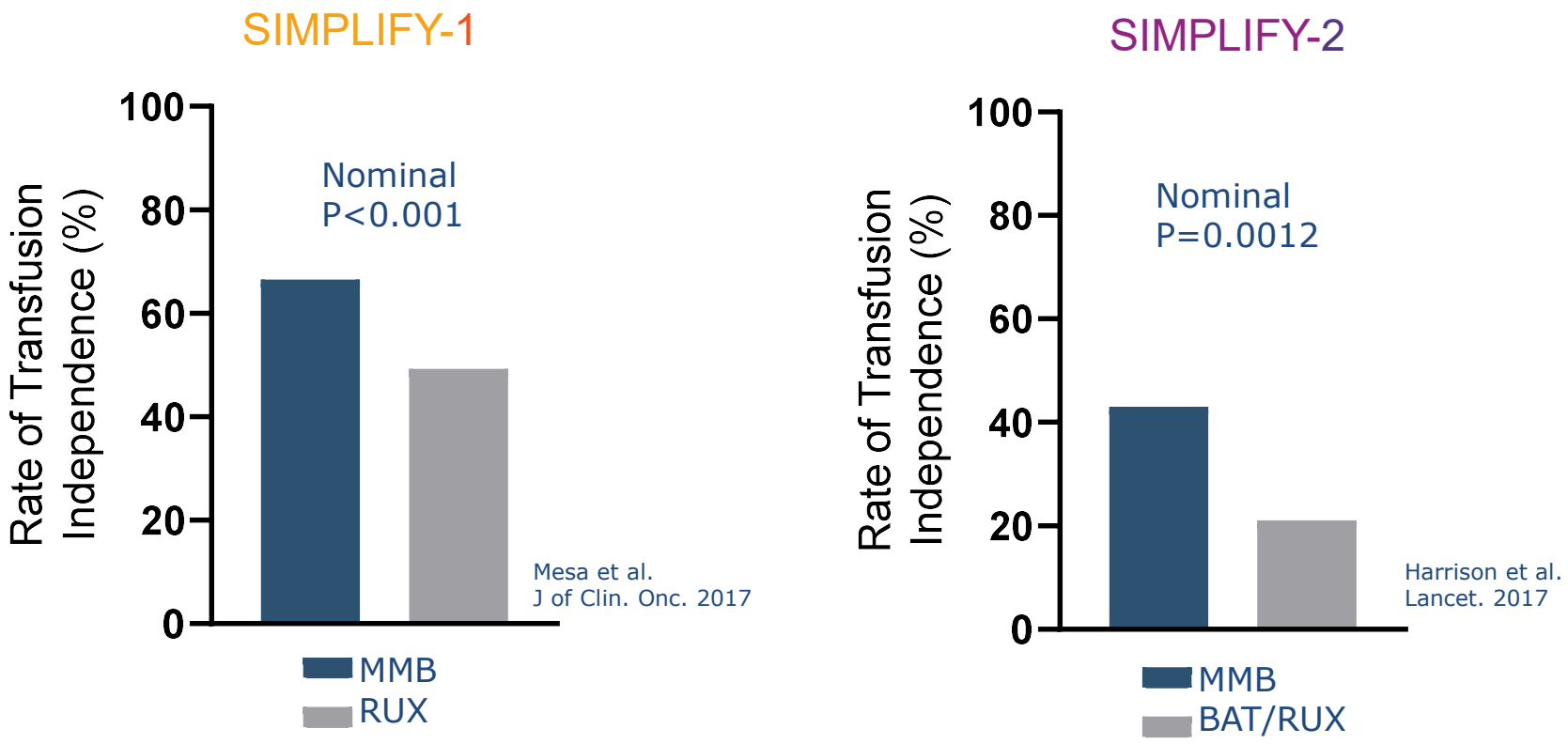
Background: Momelotinib Inhibits JAK1, JAK2 and ACVR1

- Approved JAK inhibitors (JAKi) provide spleen and symptom improvements but are generally myelosuppressive and do not address transfusion dependence (TD)
- Momelotinib (MMB) is a potent JAK1, JAK2 and ACVR1/ALK2 inhibitor with clinical activity against anemia, symptoms and splenomegaly in MF, as demonstrated in the previously conducted Phase 3 SIMPLIFY-1 & -2 trials:
  - S1: MMB vs ruxolitinib (RUX) in JAKi-naïve patients (NCT01969838)
  - S2: MMB vs best available therapy (BAT; RUX in 88% of patients) in patients with prior RUX therapy (NCT02101268)
- Preclinical and clinical translational studies have demonstrated MMB's ability to address anemia and transfusion dependency is mechanistically linked to its differentiated suppression of ACVR1/ALK2-mediated hepcidin production*



*Asshoff et al. Blood. 2017 and Oh et al. Blood Adv. 2020

Background: Transfusion Independence Response Rates for MMB vs RUX

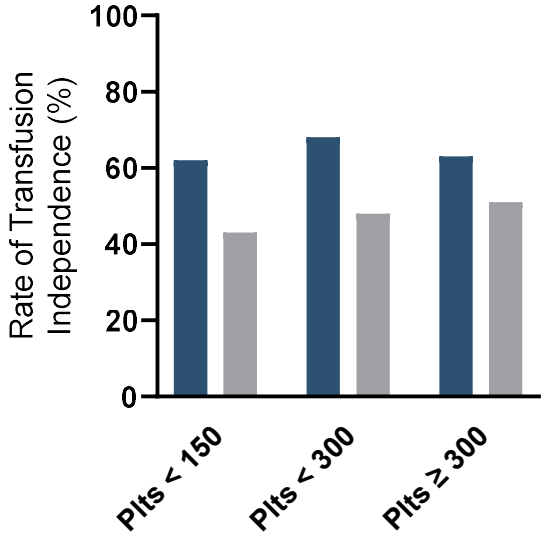


– Previously published data demonstrate higher Week-24 (W24) transfusion independence response (TI-R) rates in the MMB arms of S1 (67% vs 49%) and S2 (43% vs 21%)

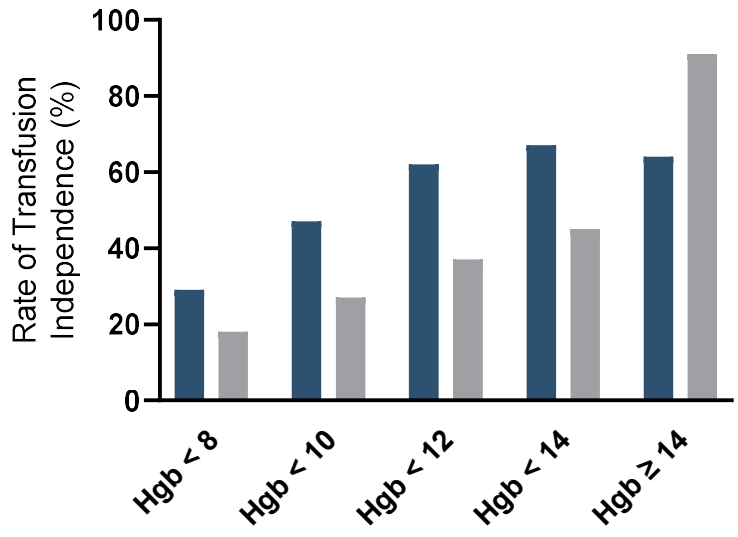
Week 24 Transfusion Independence Response (TI-R): no RBC transfusion within ≥ 12 weeks prior to Week 24, with Hgb ≥ 8 g/dL

Background: SIMPLIFY-1 Week 24 TI Response Rate for MMB vs RUX by Baseline Characteristics

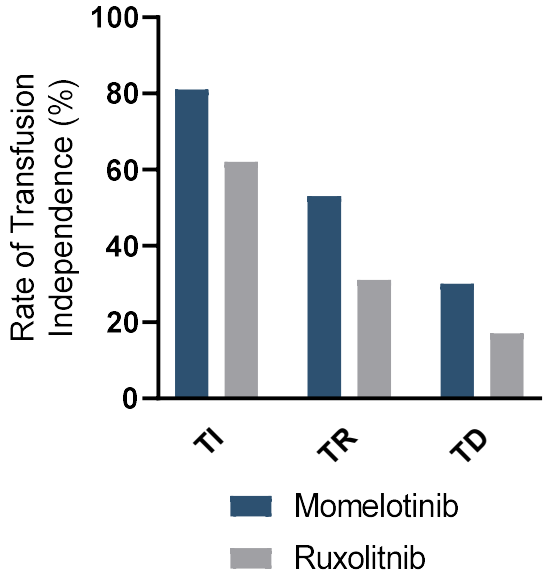
SIMPLIFY-1
W24 TI-R by Baseline PLT



SIMPLIFY-1
W24 TI-R by Baseline Hgb



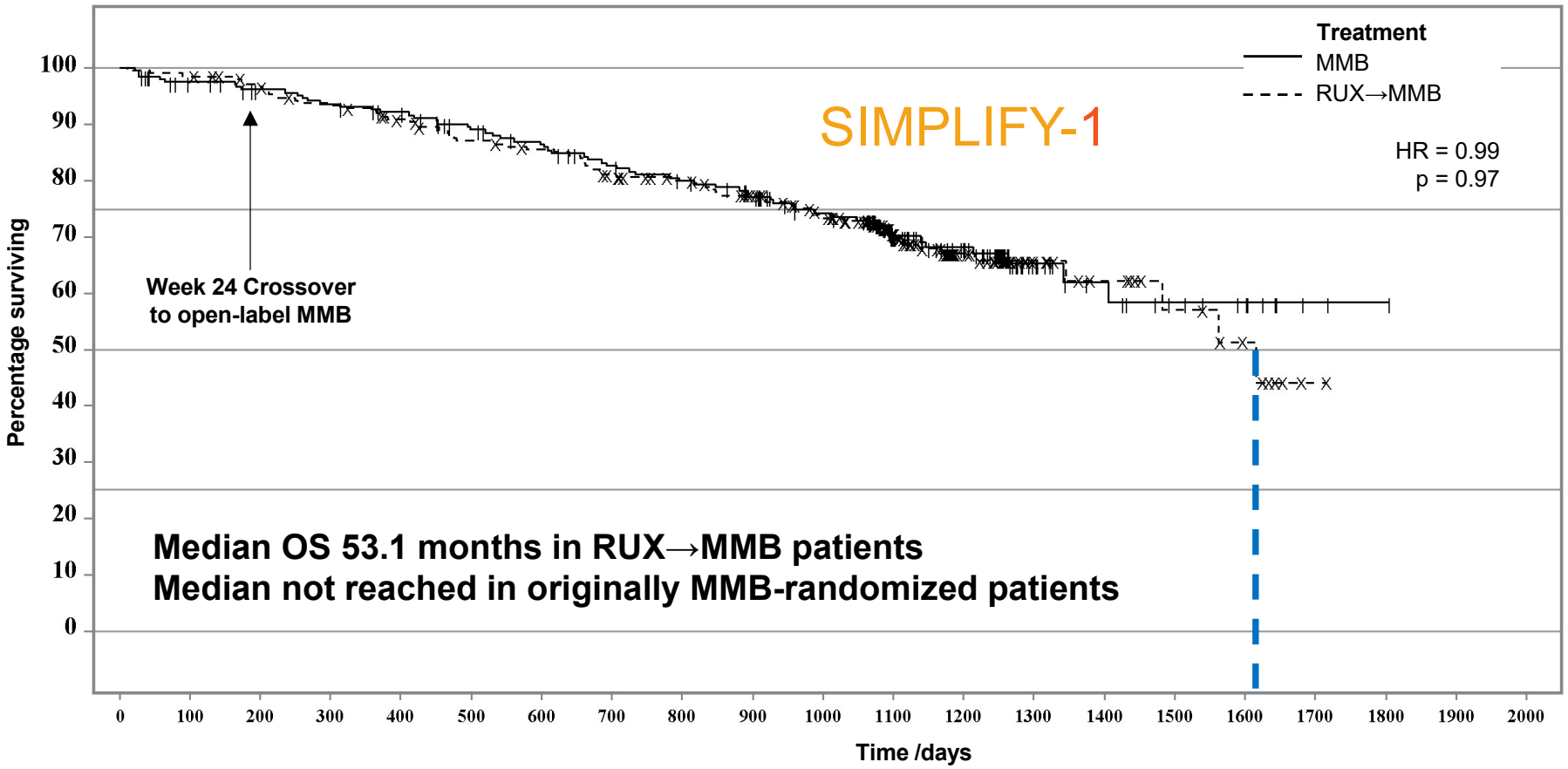
SIMPLIFY-1
W24 TI-R by Baseline Transfusion Status



- The W24 TI-R rate in S1 was higher in patients randomized to MMB vs RUX, irrespective of the degree of baseline anemia, or the baseline PLT count or transfusion status (EHA 2021 poster EP1081)

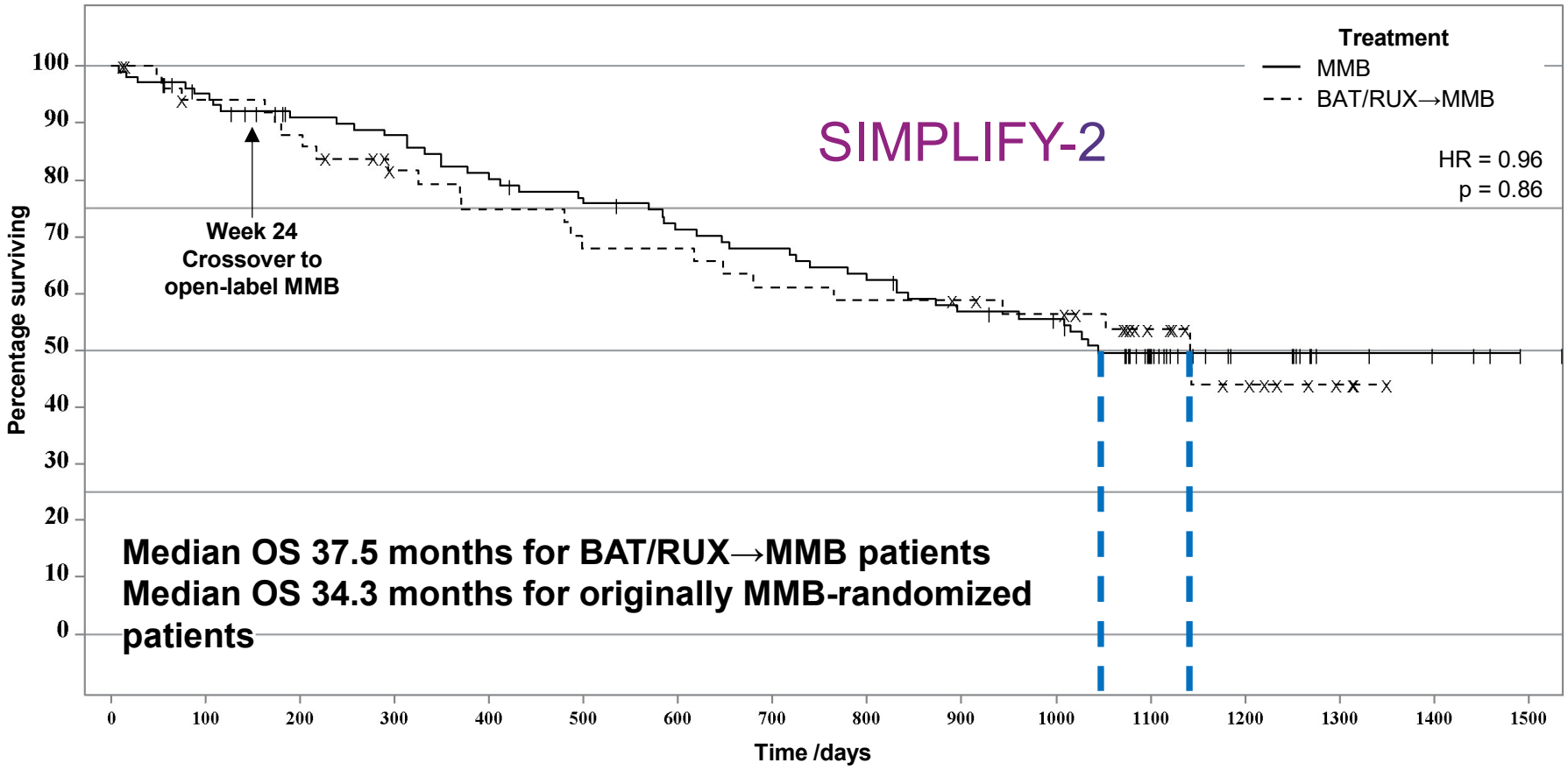
Week 24 Transfusion Independence Response (TI-R): no RBC transfusion within ≥ 12 weeks immediately prior to Week 24, with Hgb ≥ 8 g/dL
Transfusion Dependent (TD): ≥4 units of RBCs or Hgb level, ≤ 8 g/dL in the 8 weeks prior to randomization
Transfusion Independent (TI): absence of RBC transfusions and no Hgb < 8 g/dL in the 12 weeks prior to randomization
Transfusion Requiring (TR): neither TD nor TI

SIMPLIFY-1: Robust Survival for JAKi-naïve Patients



Verstovsek et. al. ASH 2020

SIMPLIFY-2: Robust Survival for Prior-JAKi Treated Patients



Verstovsek et. al. ASH 2020

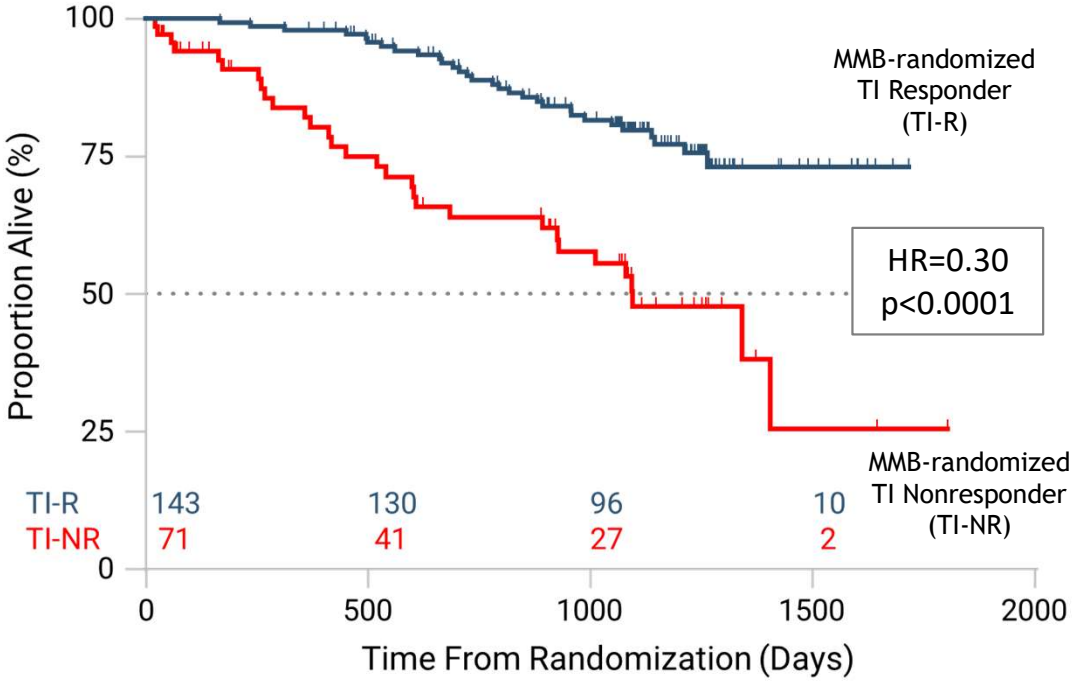
Transfusion Independence is Associated with Improved Overall Survival in Myelofibrosis Patients Receiving Momelotinib

Ruben Mesa*, Stephen T. Oh, Aaron T. Gerds, Vikas Gupta, John Catalano, Francisco Cervantes, Timothy Devos, Marek Hus, Jean-Jacques Kiladjian, Ewa Lech-Maranda, Donal McLornan, Jeanne Palmer, Uwe Platzbecker, Jacek Treliński, Kazuya Shimoda, Rafe Donahue, Bryan Strouse, Mark Kowalski, Srdan Verstovsek

*Mays Cancer Center, UT Health San Antonio, MD Anderson

- Momelotinib (MMB) is a JAK1, JAK2 and ACVR1/ALK2 inhibitor
- Previously published data from the SIMPLIFY-1 Ph3 study of MMB vs ruxolitinib in JAKi-naïve patients show higher Week-24 (W24) transfusion independence (TI) responder rates on MMB (67%) vs RUX (49%)
- Correlation between W24 TI response and overall survival observed with MMB is unique and supports the clinical relevance of TI in patients with myelofibrosis receiving MMB: **3-year survival in MMB TI responders was 80%** compared to 50% in MMB TI nonresponders

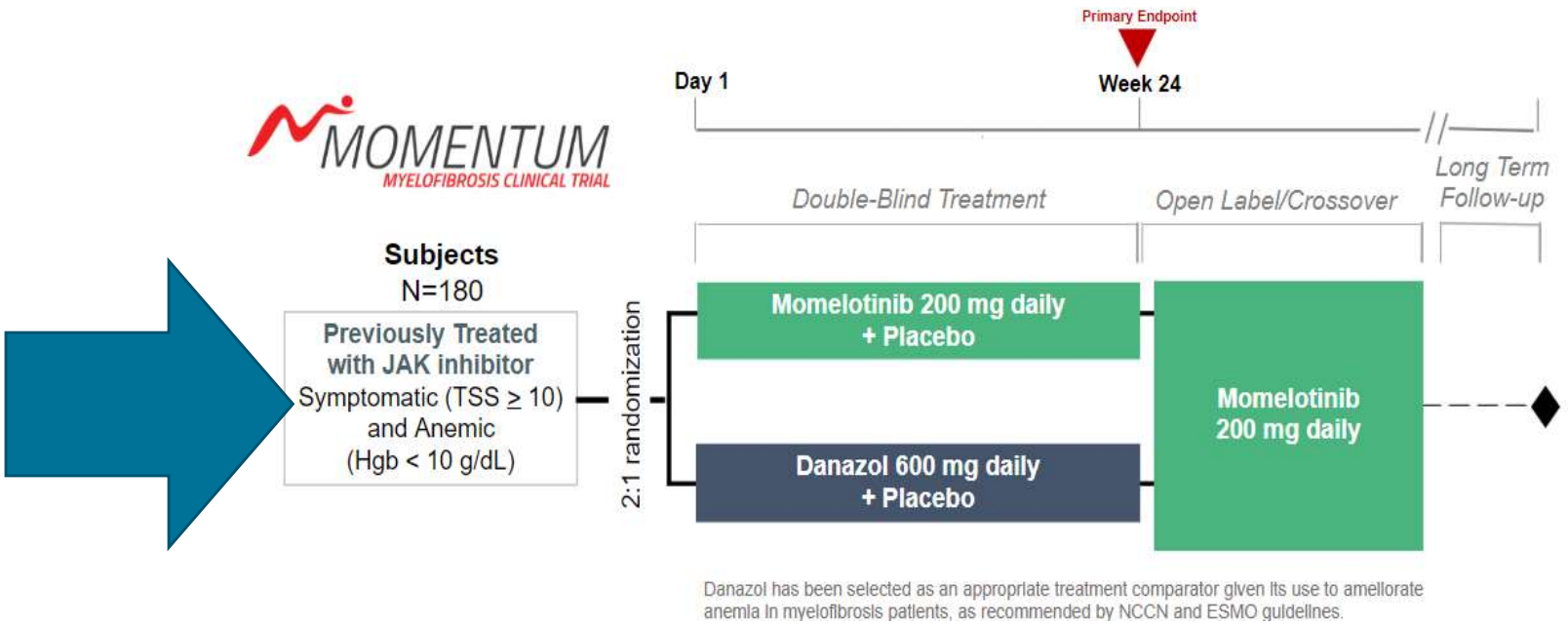
SIMPLIFY-1 Patients Randomized to MMB Who Were TI Responders at W24 Show an OS Advantage



Ongoing Phase III Trial of Momelotinib in Patients With MF

Momentum P3 Trial:
Phase 3 Registration Trial Schema

A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) versus Danazol (DAN) in Symptomatic, Anemic Subjects with Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post Essential Thrombocythemia (ET) Myelofibrosis who were Previously Treated with JAK Inhibitor Therapy



Danazol has been selected as an appropriate treatment comparator given its use to ameliorate anemia in myelofibrosis patients, as recommended by NCCN and ESMO guidelines.

FDA, US Food and Drug Administration.

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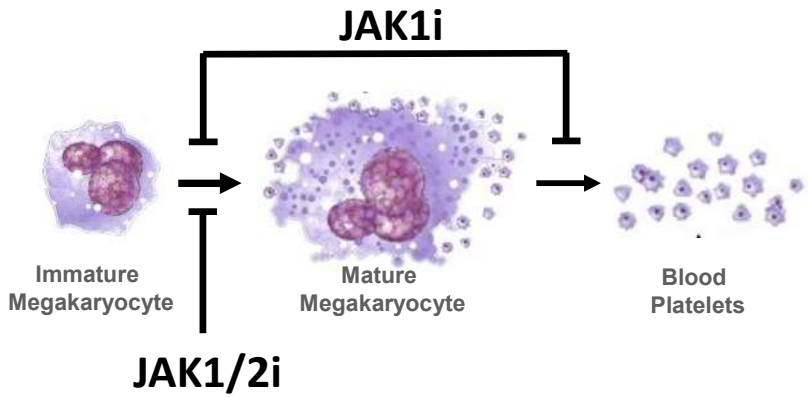
Pacritinib (PAC): A Selective Inhibitor of *JAK2* and IRAK1



JAK and FLT3 Kinases IC_{50} (nM)			
Kinase	**Pacritinib**	**Ruxolitinib**	**Fedratinib**
JAK1	1280	3.4	18
JAK2	6.0	0.0	1.1
JAK2 V617F	9.4	NR	NR
JAK3	18.3	2.0	74
FLT3	14.8	>3000	13

- JAK1/2 inhibitors impair megakaryopoiesis while preserving thrombopoiesis, whereas JAK1 inhibition impairs both megakaryopoiesis and platelet release *in vitro* and can exacerbate thrombocytopenia in MF.[a]
- Minimal JAK1 inhibition uniquely positions pacritinib for use in thrombocytopenic MF patients.

Non-Tyrosine Kinases of Interest IC_{50} (nM)			
Kinase	**Pacritinib**	**Ruxolitinib**	**Fedratinib**
CSF1R	39.5	>3000	220
IRAK1	13.6	290	620

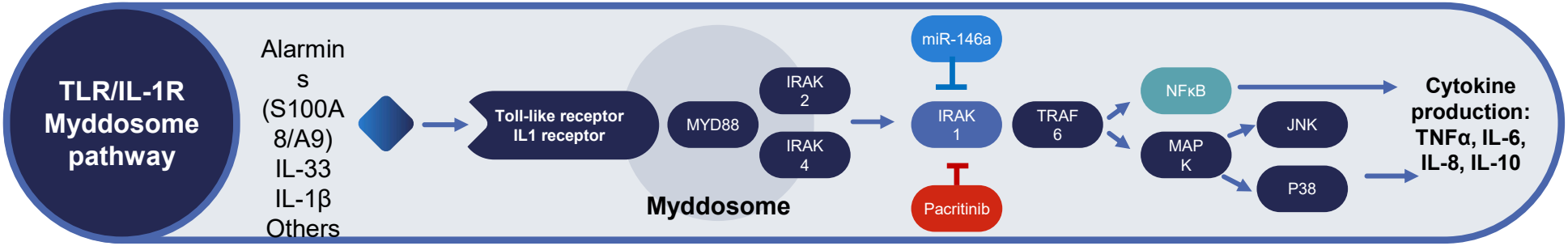
Eurofins "KINOME*scan*" for RUX and FED
J Exp Pharm publication for PAC
Leukemia publication for PAC (JAK1)

IC_{50}, half-maximal inhibitory concentration; **JAK**, Janus kinase; **TYK**, tyrosine kinase; **FLT**, FMS-like tyrosine kinase; **ITD**, internal tandem duplication; **CSF1R**, colony stimulating factor 1 receptor; **IRAK**, interleukin-1 receptor-associated kinase

[a]Jadwiga J, et. al. *Blood* (2018) 132 (Supplement 1): 2559. Mascarenhas JO, et. al. *Haematologica.* 2017; 102(2):327. Singer et al. ASH, 2014, Abstract 1874.

JAK2 Independent Mechanism

- **Inflammation** propagated by signaling through NFκβ via the TLR/Myddosome pathway was identified as a ***JAK2*-independent pathway in MF**[1-3]
- TLR signaling is constitutively active in primary MF[2], causing monocyte hyper-responsiveness to TLR ligands.[4]

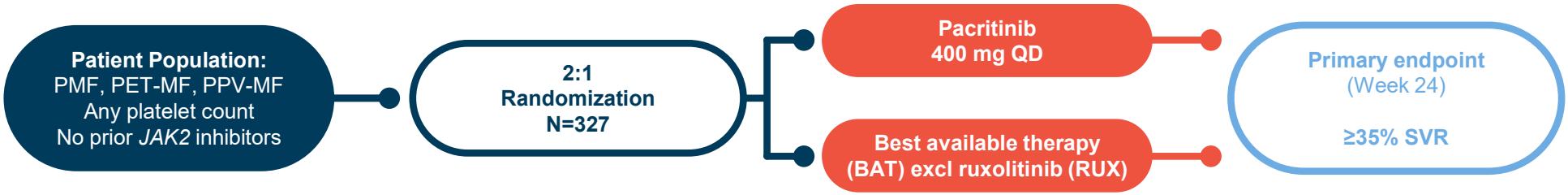


- Animal models have shown that IRAK1 is a central regulator of this pathway, and its dysregulation leads to the emergence of a cytopenic MF-like phenotype[5]
- Controlling aberrant signaling and inflammation by inhibition of IRAK1 was shown to reverse the MF phenotype[5-7]

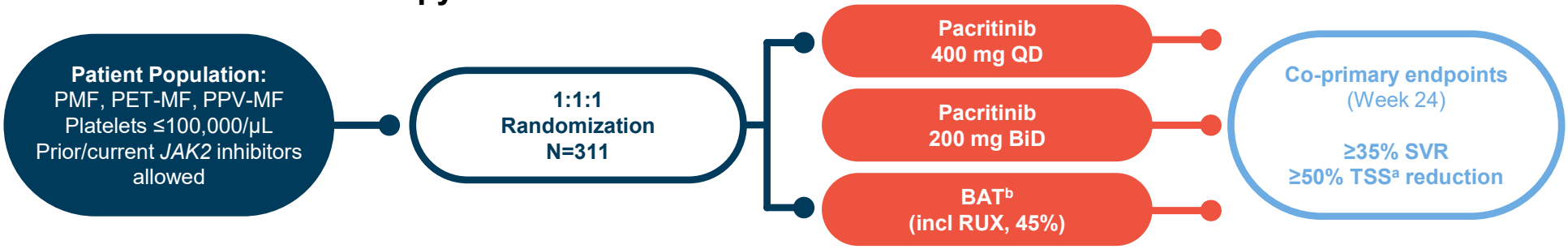
1. Fisher et al 2019, l33:29-43. 2. Lai HY et al. *Blood Adv* 2019. 3;122-130 3. Balka and De Nardo 2019. 4. Fleischman AG et al. *Blood*. 2013;122(21):4097. 5. Zhao et al. *PNAS* 2011. 6. Leimkühler et al. *Cell Stem Cell* 2020; 28:1-16. 7. Mager LF et al. *Journal Clin Investigation*. 2015.

Phase 3 Myelofibrosis Studies in First- and Second-Line Therapy

PERSIST-1[1] 1L Therapy



PERSIST-2[2] 1L & 2L Therapy



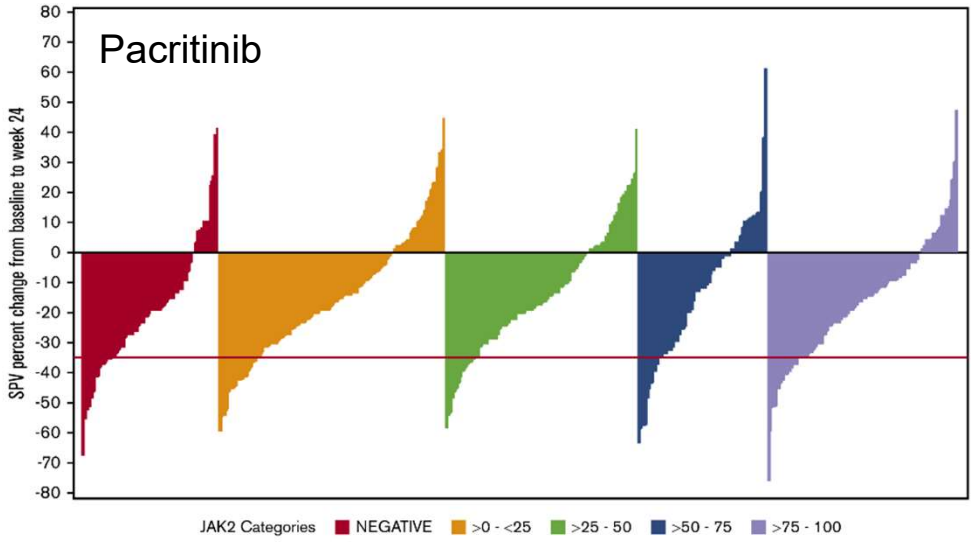
PET-MF, post-essential thrombocythemia MF; L, line; PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera MF; QD, once daily; SVR, spleen volume reduction; TSS, Total Symptom Score

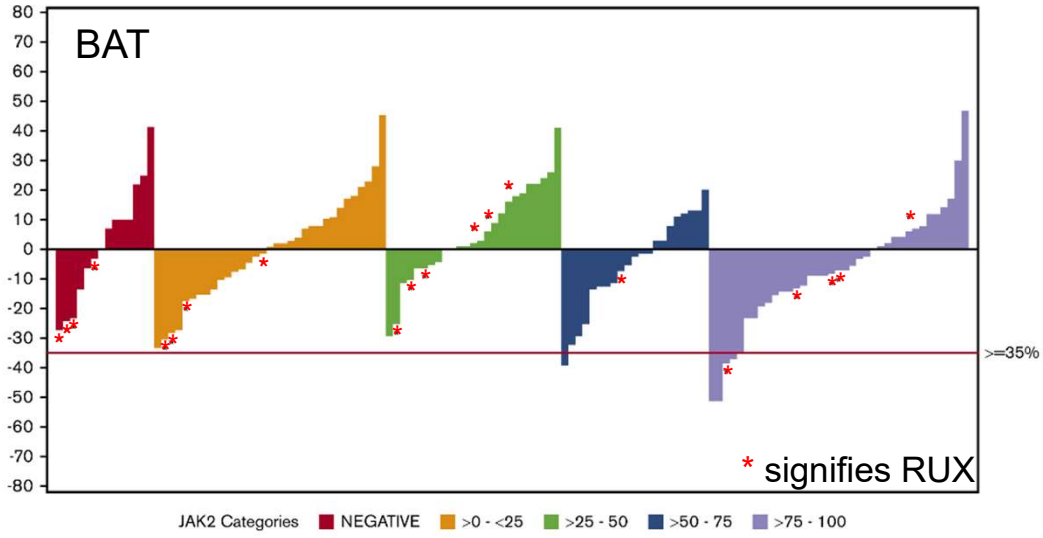
[a]TSS, total symptom score by MPN-SAF 2.0; [b]BAT includes RUX (45%)

1. Mesa RA, et al. *Lancet Haematol*. 2017;4:e225-36 2. Mascarenhas et al. *JAMA Onc*. 2017.5818.

Pacritinib Demonstrates Spleen Reduction Independent of Allele Burden in PERSIST-1/-2[1]

- PAC superior to BAT in SVR-35% response for:
  - **JAK negative** **23%** vs 0%, P=0.03
  - **4th AB quartile** **21%** vs 0%, P<0.001
  - **3rd AB quartile** **15%** vs 0%, P=0.02





1. Tremblay D et al. *Blood Advances*. 2020. 4(23):5929-35.

Pacritinib Demonstrated Efficacy in a Ruxolitinib-Naïve Moderate Thrombocytopenic Population (PERSIST-2)

Patients with Platelet Counts <100x10^9/L			
Endpoints	**Pacritinib 200 mg BiD, (N=43)**	**BAT[a] (N=39)**	***P* value vs BAT**
≥35% SVR (ruxolitinib-naïve patients)	28%	3%	0.002
≥50% reduction in TSS (ruxolitinib-naïve patients)	33%	13%	0.04

- **82% (32 pts) of the BAT arm was on ruxolitinib**

BAT, best available therapy. SVR, spleen volume reduction. P-value from Fisher Exact Test.
[a]BAT includes RUX (45%)
Harrison et al. EHA2017_Poster P701.

Efficacy with Severe Thrombocytopenia (SVR)

SVR response maintained in patients with severe thrombocytopenia

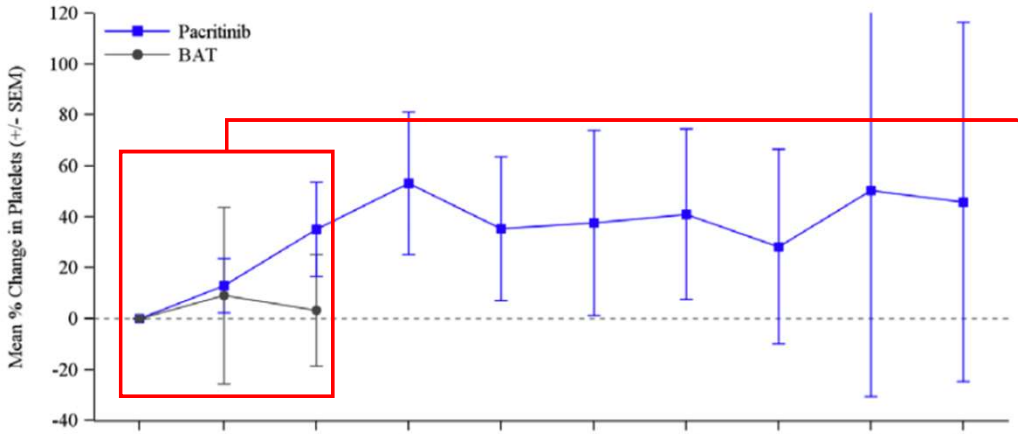
Spleen Volume Response: PERSIST-1/-2 Pooled Data				
	Pooled PAC (all doses)	Pooled PAC (400 mg QD)	PAC 200 mg BiD	Pooled BAT
Platelet count <50×10⁹/L				
≥35% SVR (%, n)	**23%** (24/104)	**21%** (15/73)	**29%** (9/31)	**2%** (1/48)
P value vs BAT	0.0007	0.0025	0.0059*	-
Overall Population				
≥35% SVR (%, n)	**19%** (69/369)	**18%** (53/295)	**22%** (16/74)	**4%** (7/179)

**P* value compared to BAT from PERSIST-2

Mesa R et al. ASH 2019 (abstr 4195).
Unpublished data

PERSIST-1: Platelet Stability in Patients with Severe Baseline Thrombocytopenia

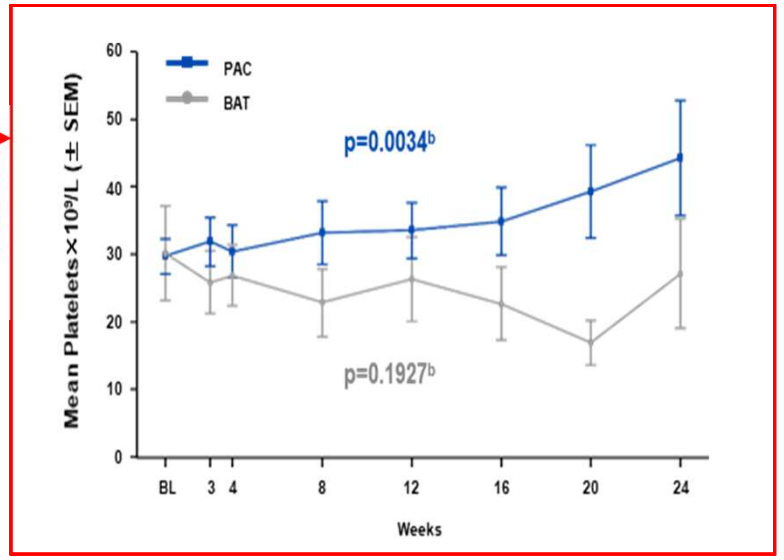
Percent change in platelet counts over time
(baseline PLT count <50×10⁹/L)



Number of Subjects

Pacritinib	33	25	19	13	13	10	11	10	5	4
BAT	14	10	7							

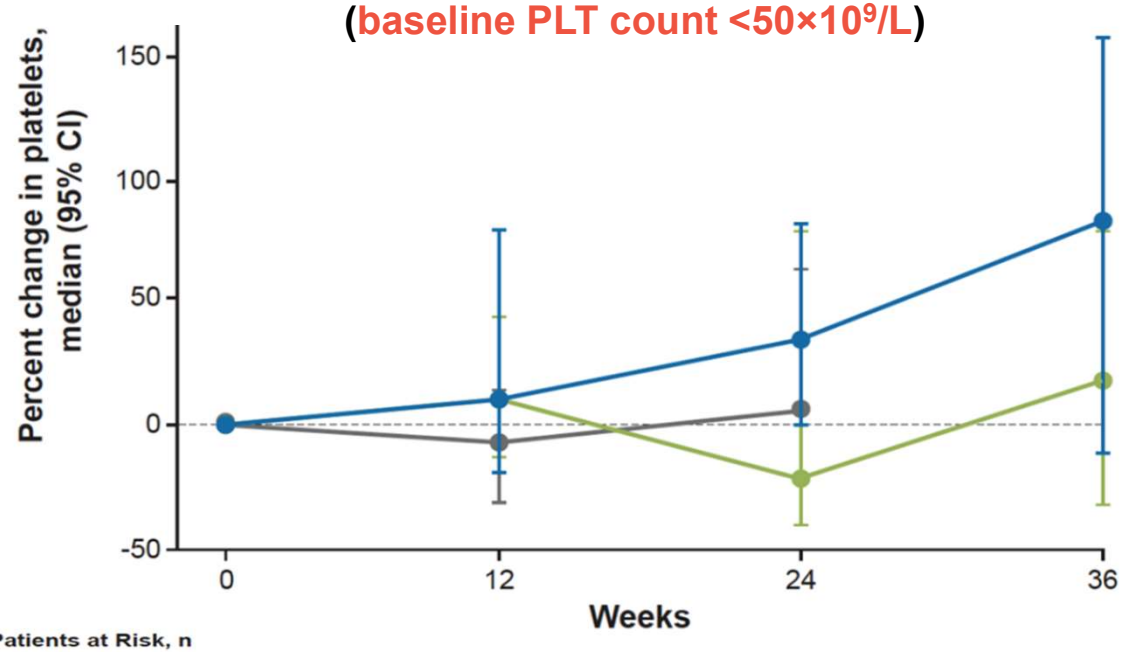
Trend over first 24 weeks
(baseline PLT count <50×10⁹/L)



PERSIST-1 CSR

PERSIST-2: Platelet Stability in Patients with Severe Baseline Thrombocytopenia

Percent change in platelet counts
(baseline PLT count <50×10^9/L)

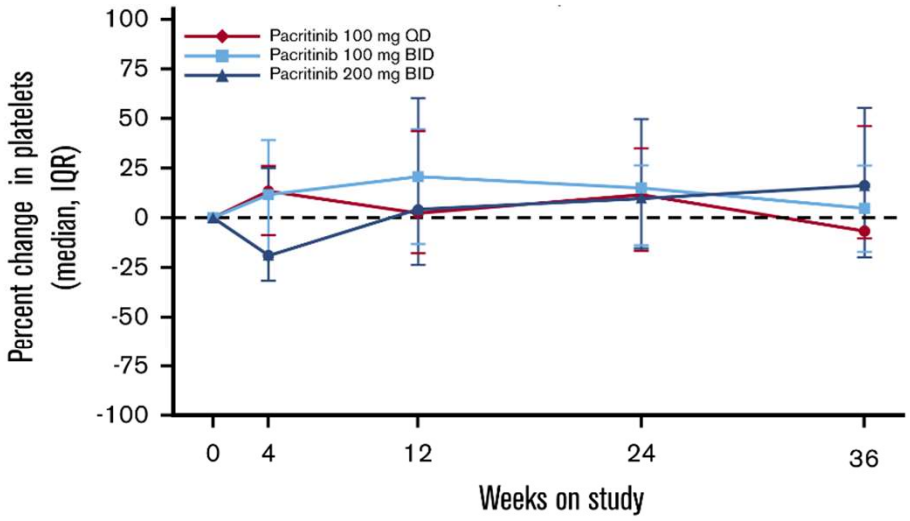


Patients at Risk, n				
Pacritinib 400 mg Once Daily	50	28	19	10
Pacritinib 200 mg Twice Daily	47	32	16	11
BAT	42	23	12	

BAT includes RUX (45%)
Mascarenhas et al. PERSIST-2 eFig7

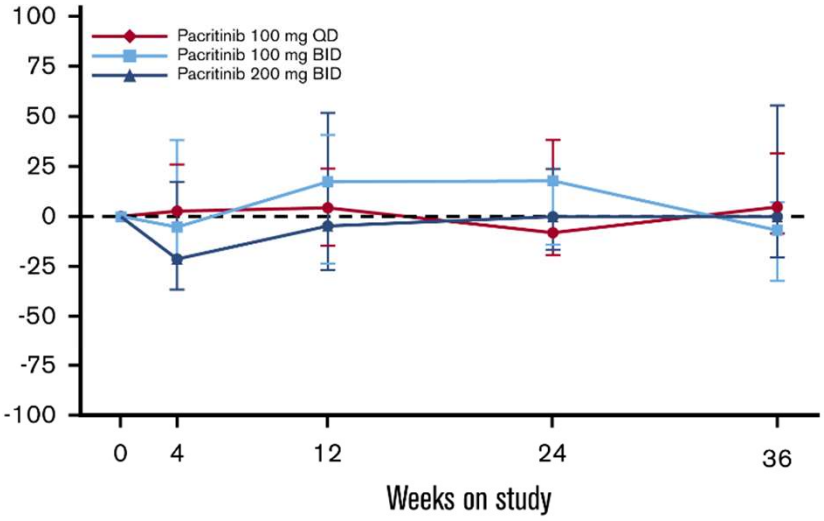
PAC203: Platelet Count Stability Overall & in Patients With Severe Baseline Thrombocytopenia

Percent change in platelet counts (overall population)



Number of Subjects					
Pacritinib 100 mg QD	52	44	37	22	11
Pacritinib 100 mg BID	55	49	42	24	16
Pacritinib 200 mg BID	53	49	38	26	14

Percent change in platelet counts (baseline PLT count <50×10^9/L)

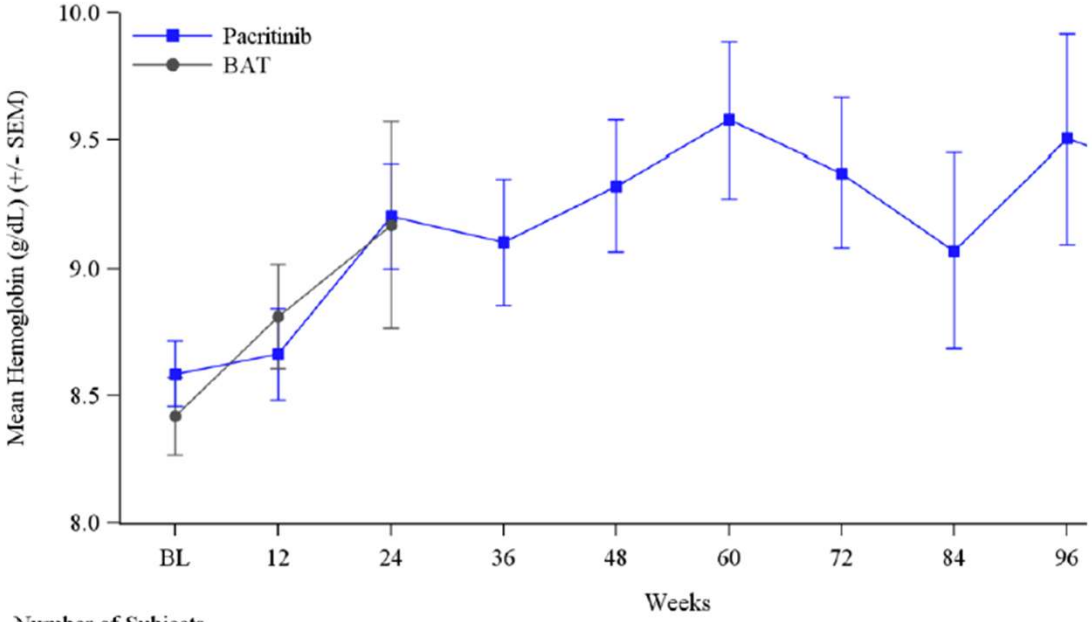


	23	23	16	8	4
	24	23	19	9	6
	24	24	20	13	9

Gerds A et al. *Blood Advances.* 2020;4:5825-5835.

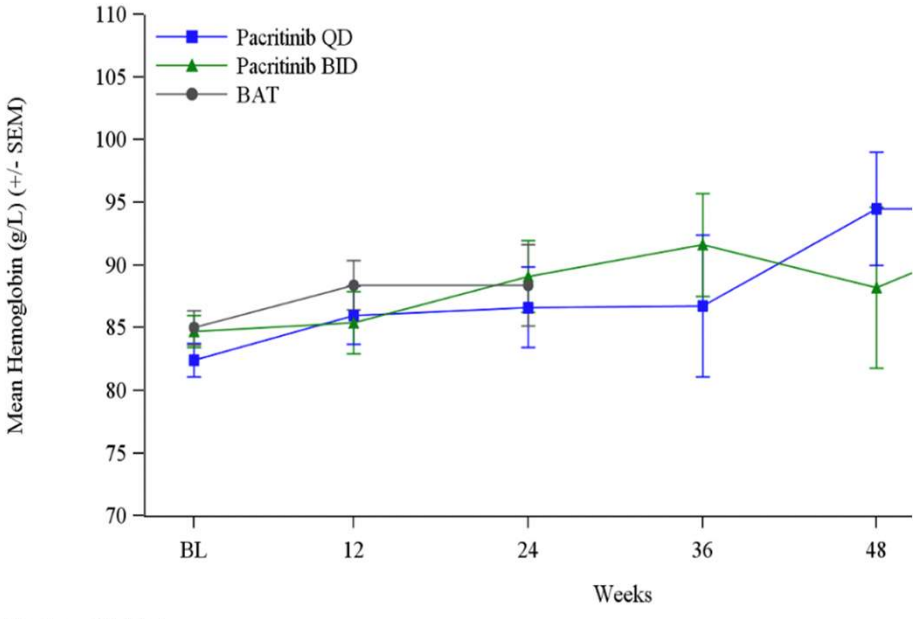
PERSIST-1/-2: Hematologic Stability / Improvement

PERSIST-1: mean Hgb levels (baseline Hgb <10 g/dL)



Number of Subjects									
Pacritinib	84	71	56	44	41	33	28	23	15
BAT	46	40	24						

PERSIST-2: mean Hgb levels (baseline Hgb <10 g/dL)



Number of Subjects					
Pacritinib QD	65	39	26	12	2
Pacritinib BID	62	44	26	15	5
BAT	54	38	19		

BAT in PERSIST-2 includes RUX (45%)
Left: PERSIST-1 CSR. Right: PERSIST-2 CSR Fig 14.3.2.4.7

A selection of novel agents/targets being developed in MPN particularly MF

Cell-cycle Checkpoint

- P2 Imetelstat | Telomerase Inhibitor (*Geron*)
- P1 Alisertib | Aurora Kinase Inhibitor (*Takeda*)

Anti-fibrotic

- P2 PRM-151 | Pentraxin-2 (*Promedior*)

Receptor Ab / ADC

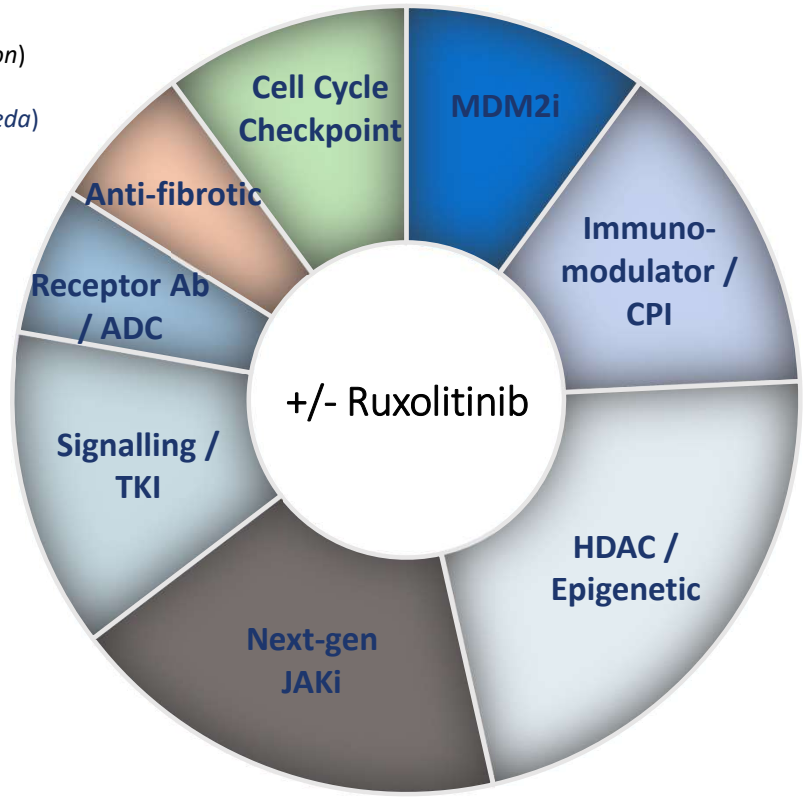
- P2 SL-401 | CD123-toxin (*Stemline*)

Signaling / TKI

- P2 Glasdegib | Hedgehog (*Pfizer*)
- P2 Sonidegib | Hedgehog (*Sun*)
- P2 INCB'465 | PI3Ki (*Incyte*)
- P2 LCL1 I SMAC/IAP (Novartis)

Next-gen JAKi

- P3 Fedratinib | JAK2 (*Celgene*)
- P3 Pacritinib | JAK2/FLT3 (*CTI Bio*)
- P3 Momelotinib | JAK2/1/ACVR1 (*Sierra*)
- P2 Itacitinib | JAK1 (*Incyte*)



Slide Courtesy of Prof Claire Harrison

Apoptosis/MDM2/BCL

- P1 KRT-232 (*Kartos Therapeutics*)
- P2 Idasanutlin / RG7388 (*Roche*)
- P1 Navitoclax | BCL2 inhibition (*Abbvie*)

Immuno-modulator / CPI

- P3 Pegasys | IFN-α2a (ESR/Roche)
- P3 Ropeg-IFN-α2b (*PharmaEssentia*)
- P2 Nivolumab / Pembrolizumab | PD-1 (*BMS / MRK*)

HDAC / Epigenetic

- P3 Azacytidine | HMA (*ESR/Celgene*)
- P3 Panobinostat | HDAC (*Novartis*)
- P2 Givinostat I HDAC (Italfama)
- P2 IMG-7289 | LSD1 (*Imago*)
- P1 CPI-0610 | BETi (*Constellation*)
- P1 PU-H71 | HSP90i (*Samus*)

PHASE OF DEVELOPMENT (IN MPN): P1 P2 P3

Selected Additional Single Agent Trials in Myelofibrosis

Agent	Drug Class	Phase
LCL-161	Smac-mimetic (IAP antagonist)	2
Alisertib	AURKA inhibitor	N/A
Tagraxofusp	CD123-targeting fusion protein	2
KRT-232	HDM2 inhibitor	2
Bomedemstat	LSD1 inhibitor	2
CPI-0610	BET inhibitor	2
Imetelstat	Telomerase inhibitor	2
PRM-151	Recombinant human pentraxin-2	2
Nivolumab/pembrolizumab	Anti-PD1 antibodies	2
Selinexor	SINE	2

Bose P, Verstovsek S. *Leuk Lymphoma.* 2020;61(8):1797-1809.

Selected JAKi-Based Rational Combinations

Accelerated/blastic phase

Cytopenia (ANEMIA)

Higher Responses In Spleen and Symptoms

Drug	Mechanism of Action	Phase
Azacitidine	HMA	2
Decitabine	HMA	2
Luspatercept	Activin receptor ligand rap	2
Danazol	Androgen	2
Thalidomide	IMiD	2
Pomalidomide	IMiD	1/2
PEG-IFNa-2a	–	1/2
PU-H71	HSP90i	1/2
Itacitinib	JAK1i	2
Navitoclax	BCL-2/BCL-xL	2
Parsaclisib/umbralisib	PI3Kδi	2
KRT-232	MDM2i	1/2
CPI-0610	BETi	2
Pevonedistat	NAEi	1

Ongoing or planned Phase 3 studies in Myelofibrosis

Agent	Drug Class
Momelotinib	JAK1/2 inhibitor
Pacritinib	JAK2 inhibitor
Fedratinib	JAK2 inhibitor
KRT-232	HDM2 inhibitor
Navitoclax	BCL-xL inhibitor
CPI-0610	BET inhibitor
Imetelstat	Telomerase inhibitor
Luspatercept	Activin receptor ligand rap

New Drugs - MF

- Burden of Having MF
- JAK Inhibitors
- New Drugs Front Line
- New Drugs Second Line
- Future State

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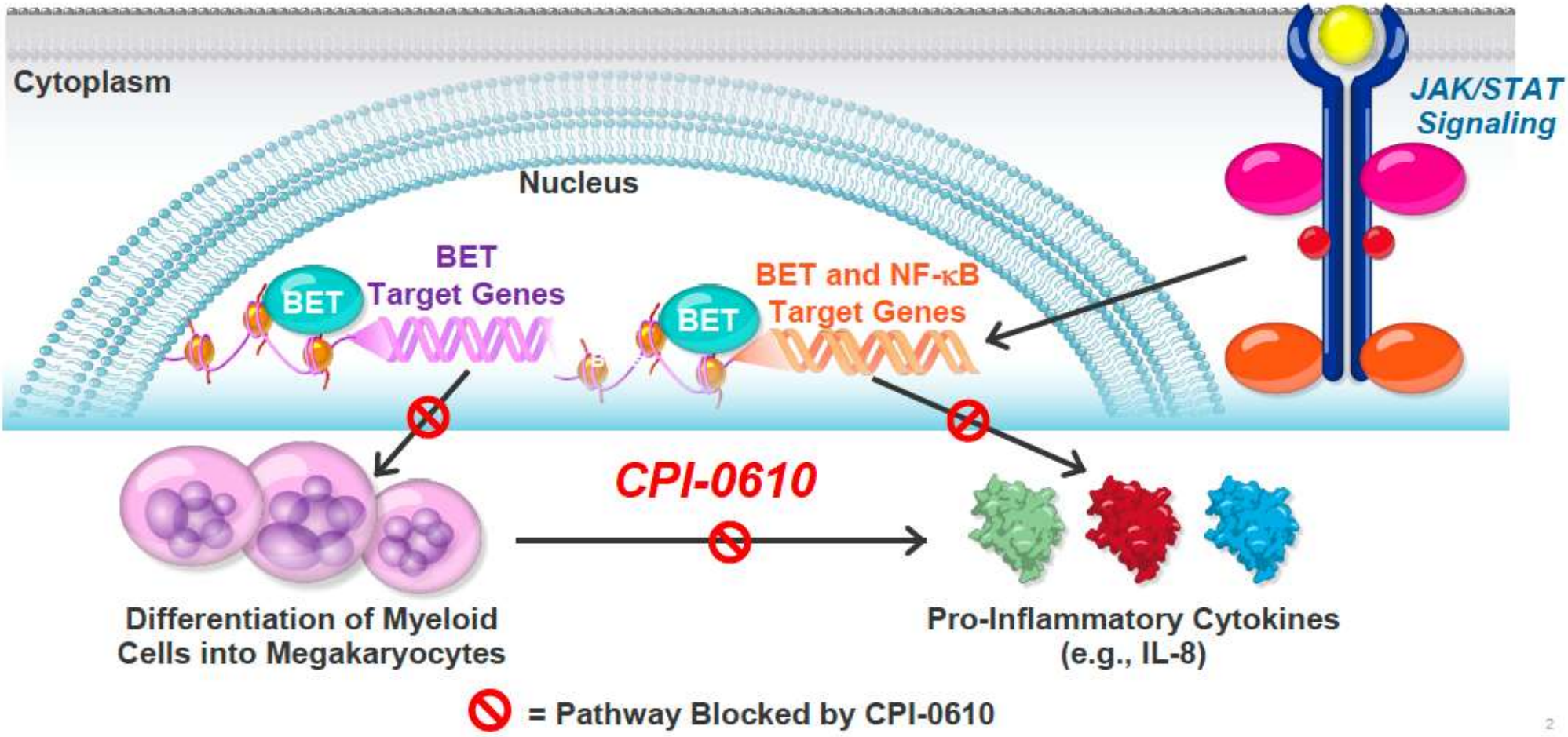
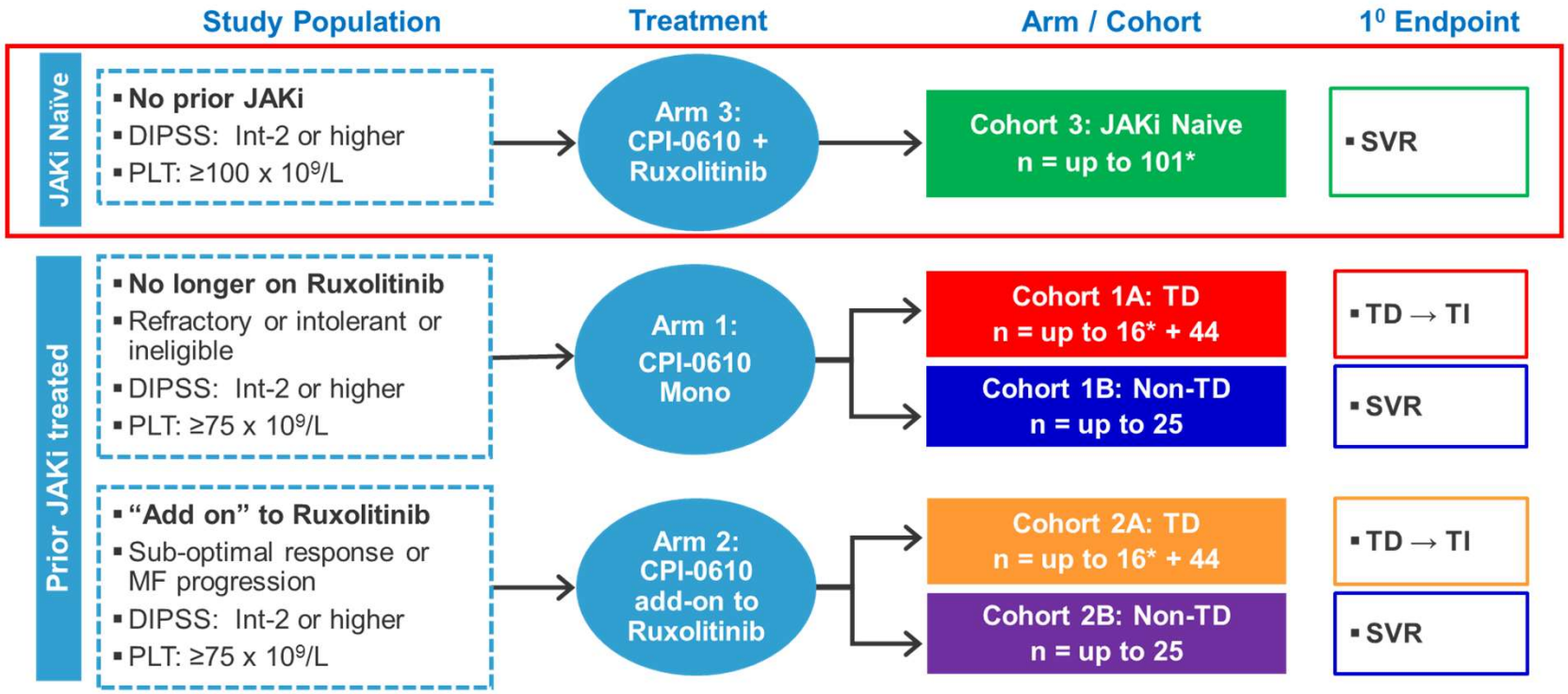
Mechanism of Potential Disease Modification in Myelofibrosis

Reduce Inflammation and Suppress Cells in the Bone Marrow That Drive MF (Megakaryocytes)



Mascarenhas et. al.
ASH 2019

MANIFEST: Phase II Study of CPI-0610 in JAK Inhibitor–Naïve Patients



DIPSS: Dynamic International Prognostic Scoring System, TD = Transfusion Dependent; TI = Transfusion Independent; SVR = Spleen Volume Response; PLT: Platelet
ClinicalTrials.gov Identifier: NCT02158858 for further details on study design and patient population
Preliminary data as of 17 October 2019
* Will follow Simon 2-stage design

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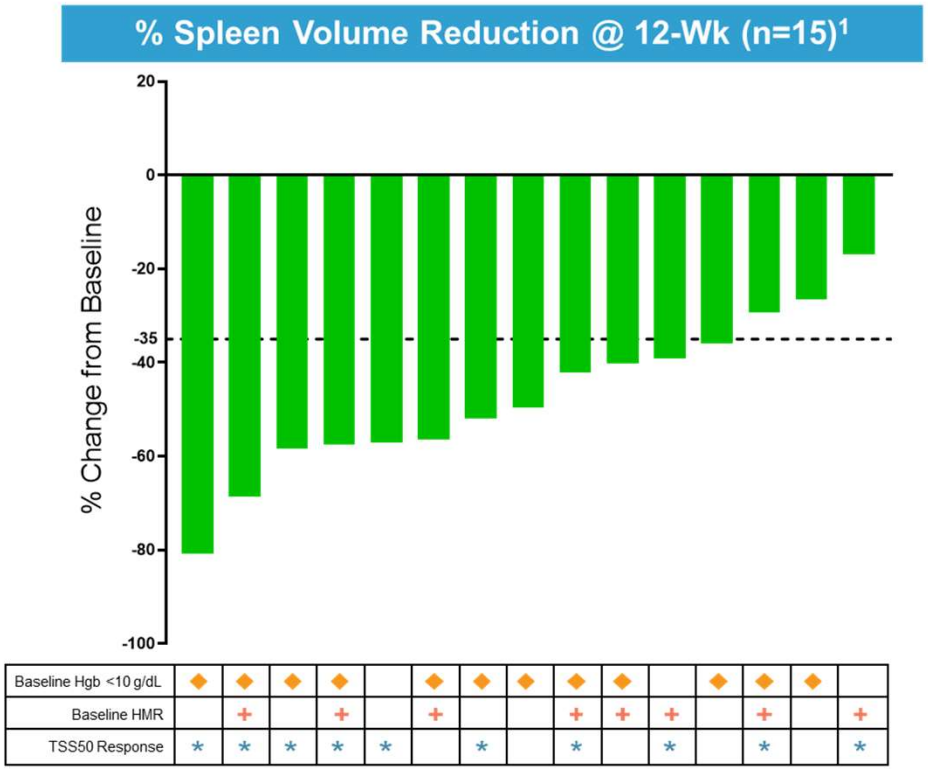
MANIFEST: Spleen Volume Reduction at 12 Weeks



- 80% (12/15)[1] SVR35 response at 12-Wk
  - Median % Change at 12-Wk: -49.7% (range: -80.8%, -17%)
- The response was seen in a population that was high risk:
  - 86.7% of patients[1] DIPSS ≥Int-2
  - 80% of patients[1] Hgb < 10g/dL
  - 53.3% of patients[1] HMR positive
- Median Rux Dose[2]: 10mg BID
- In JAKi naïve patient population, the benchmark for SVR35 response is 28.5-41.9%[3]

[1] Evaluable patients: Patients received at least 12 week of treatment, have baseline and post-baseline SVR assessment at 12-Wk.
SVR35 Response: ≥35% Spleen Volume Reduction
TSS50 Response: ≥50% improvement in Total Symptom Score (MFSAF v.4)
HMR: Patient with ≥ 1 HMR mutation
[2] Rux dose for longest duration during 12 weeks
[3] JAKAFI (ruxolitinib) [Package insert]

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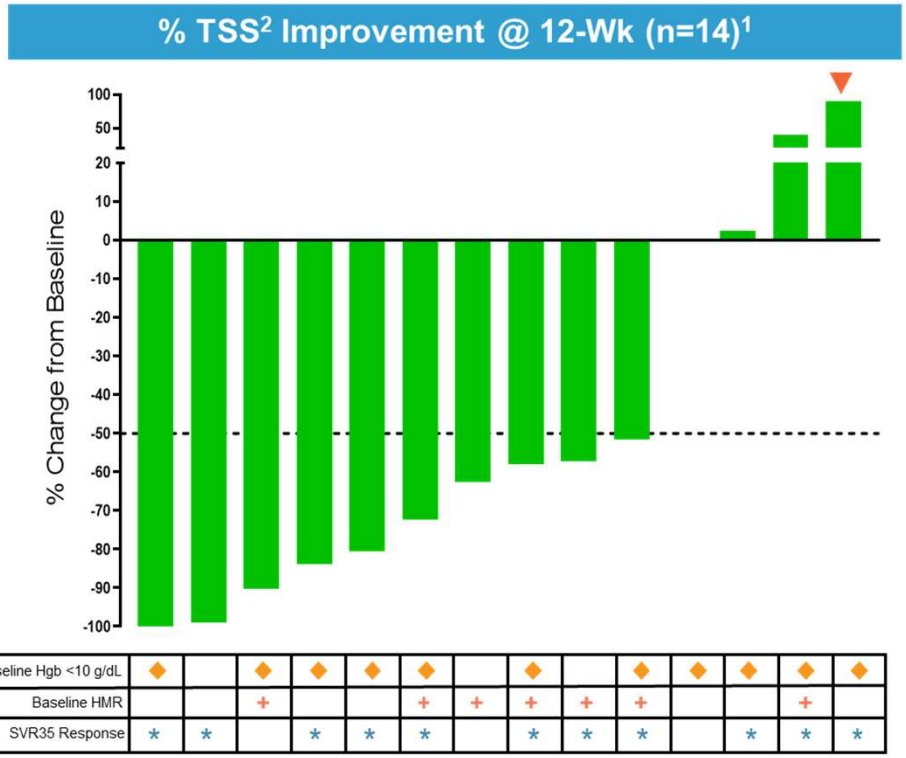
MANIFEST: Total Symptom Improvement at 12 Weeks



[1] Evaluable patients: Baseline and 12 Wk data available. One patient TSS non-evaluable due to missing baseline.
TSS50 Response: ≥50% improvement in Total Symptom Score (MFSAF v4)
SVR35 Response: ≥35% Spleen Volume Reduction
HMR: Patient with ≥ 1 HMR mutation
[2] JAKAFI prescription label

- 71.4% (10/14) patients had TSS50 Response at 12-Wk
  - Median % Change at 12-Wk: -60.3% (range: -100%, 90%)
- In JAKi naïve patient population, the benchmark for TSS50 response is 45.9%[2]

▼ Patient had dose interruption due to AE; 41.7% reduction in TSS at Week 6 prior to dose interruption

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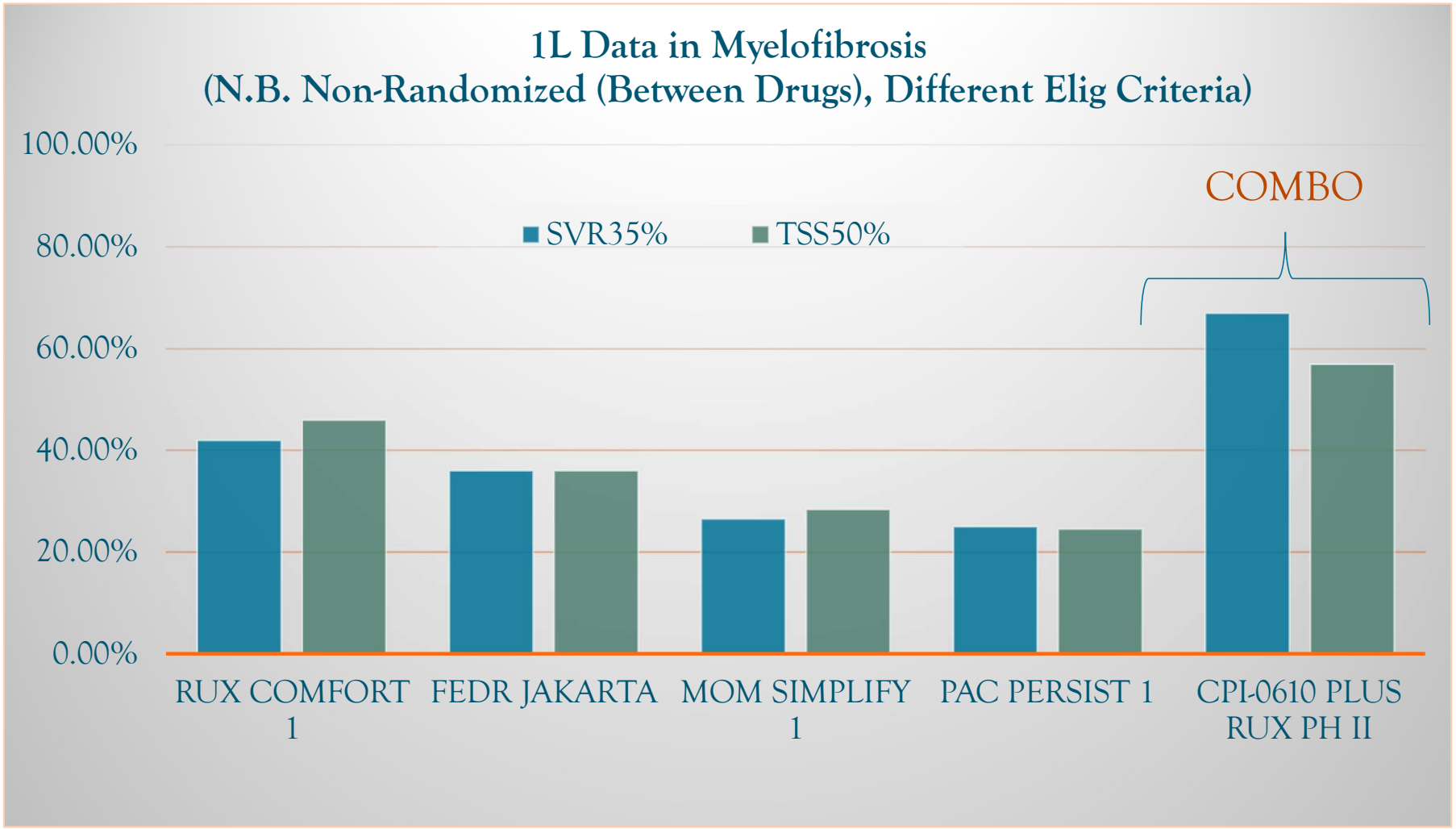
Comparison for 1L MF Therapy



Verstovsek et. al. NEJM 2012
Pardanani et. al. JAMA Inc 2015
Mesa et. al. JCO 2017
Mesa et. al. Lancet Hematology 2017
Mascarenhas et. al. ASH 2020

New Drugs - MF

- Burden of Having MF
- JAK Inhibitors
- New Drugs Front Line
- New Drugs Second Line
- Future State

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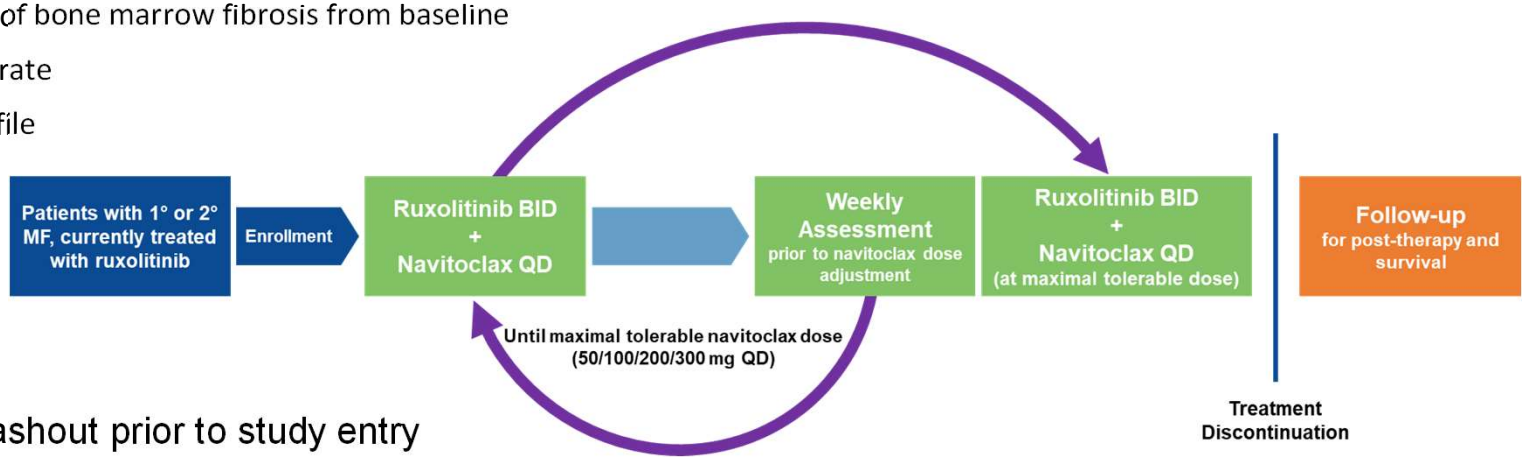
Navitoclax + Ruxolitinib: Study Design

Primary Endpoint: Evaluate navitoclax + ruxolitinib combination on spleen volume from baseline at week 24

Secondary Endpoints: Assess effect of navitoclax + ruxolitinib combination on

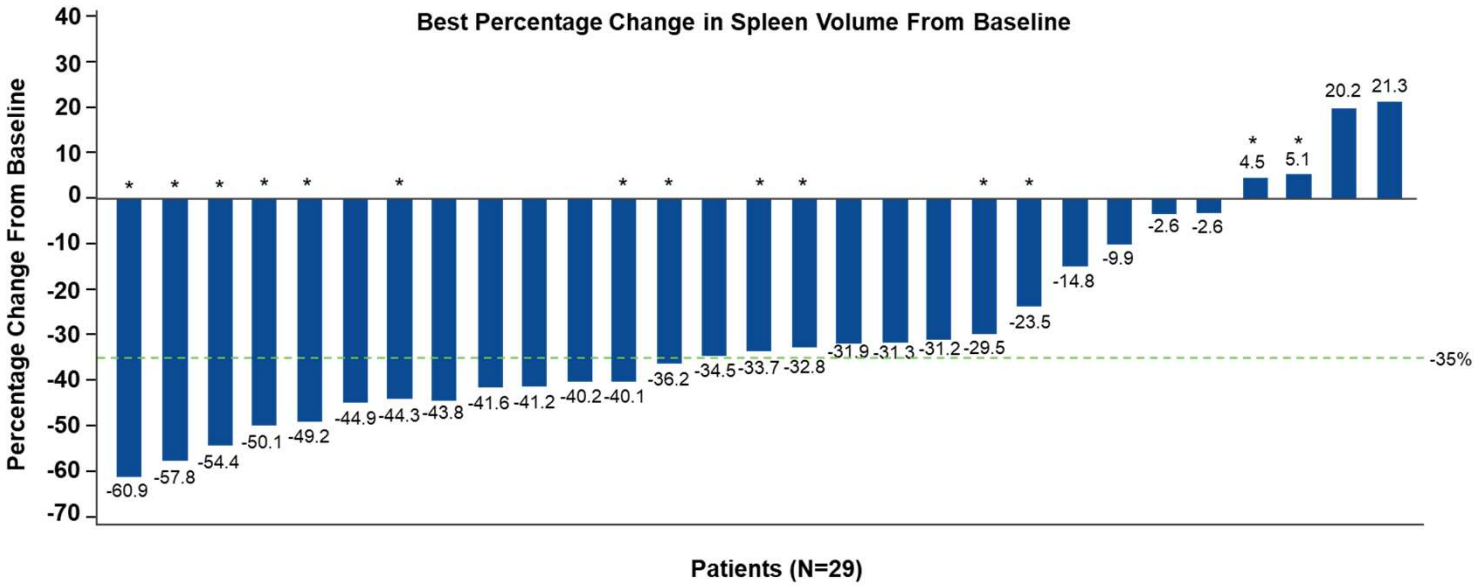
- Total symptom score
- Change in degree of bone marrow fibrosis from baseline
- Anemia response rate
- Safety and PK profile



- No ruxolitinib washout prior to study entry
- Navitoclax administration starting dose: 50 mg QD
- Dose was increased weekly in a stepwise fashion up to a maximum of 300 mg QD
  - On the basis of individual tolerability and platelet count

BID, twice daily; QD, once daily.

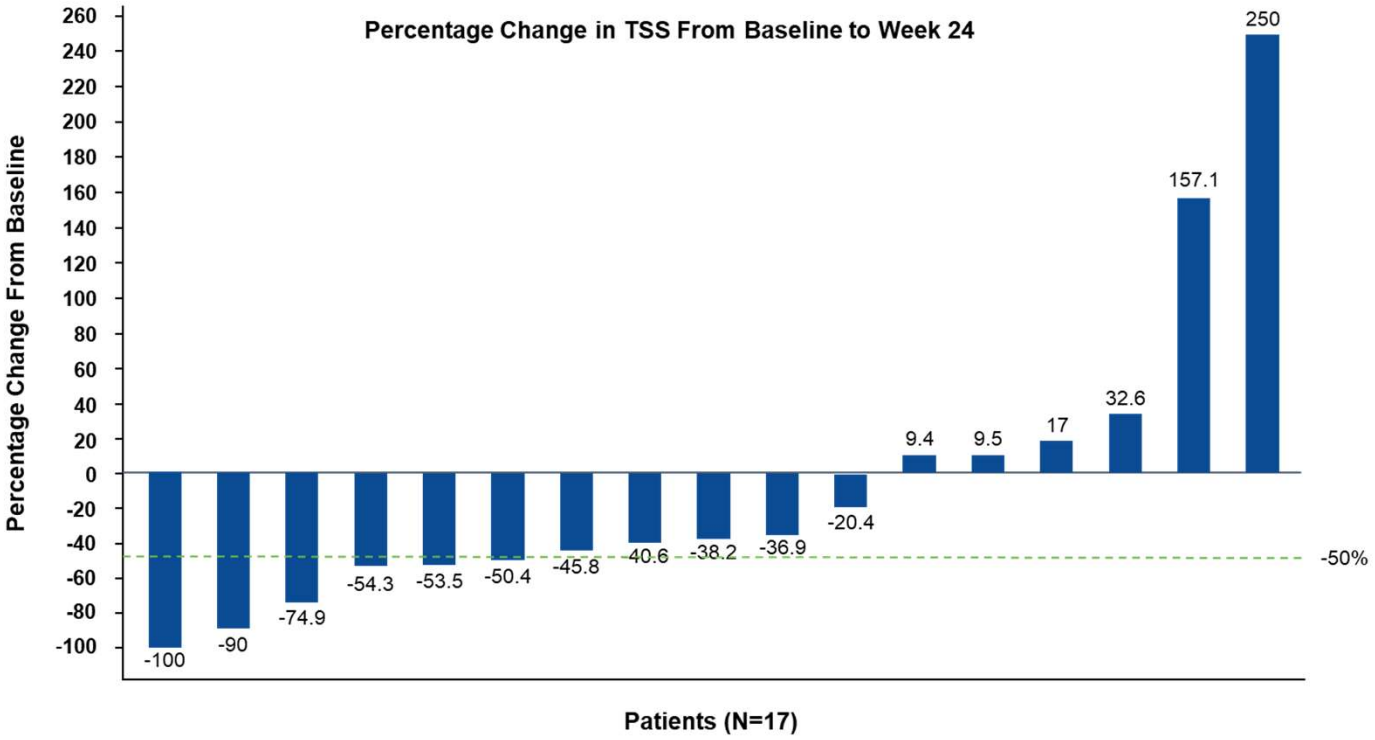
Navitoclax Overcomes Ruxolitinib Resistance, Resulting in Splenomegaly Improvement for Most Patients



- SVR_{35} best on study: 43% (13/30)
- SVR_{35} at week 24: 30% (9/30)
- 53% (16/30) of patients resolved palpable splenomegaly during study treatment
- 25% (8/32) of patients demonstrated reduction in bone marrow fibrosis (local assessment)
  - 13% (4/32) with 1 grade reduction
  - 13% (4/32) with 2 grade reduction

Data cut-off: November 18, 2019.
Percentages calculated on the basis of efficacy analysis set (N = 30).
Baseline is defined as the last non-missing observation collected on or prior to the date of the first dose of any component of study treatment.
*Denotes patients with high molecular risk (defined by the presence of mutations within *ASXL1*, *EZH2*, *IDH1/2*, *SRSF2*, *U2AF1*).

Navitoclax Overcomes Ruxolitinib Resistance, Resulting in Total Symptom Score Improvement for Most Patients

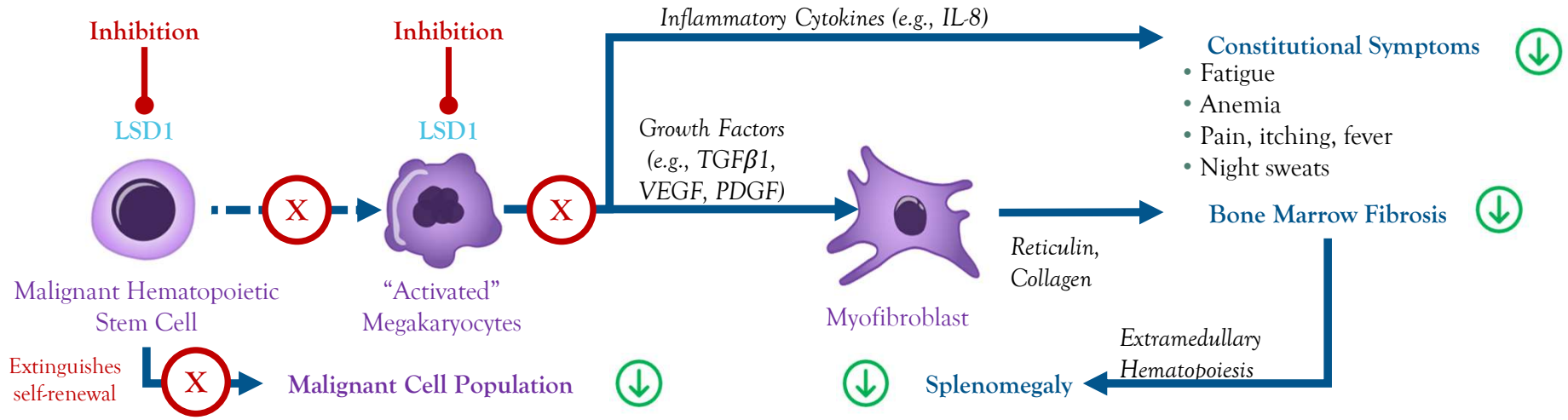


- 65% (11/17) of patients experienced reduction in symptoms
- 35% (6/17) of patients experienced ≥50% reduction in symptoms
- Baseline median TSS: 12 (range, 0-30)
- Week 24 median TSS: 7 (range, 0-23)

Data cut-off: November 18, 2019.
N = number of patients with non-missing percentage change in TSS from baseline at week 24 (missing baseline TSS: n = 5; missing week 24 TSS: n = 7; baseline TSS = 0: n = 1).
Baseline is defined as the average value of the observation collected on or prior to the date of the first dose of any component of study treatment.

LSD1 Inhibition has Strong Therapeutic Rationale in MPNs

- LSD1 inhibition impairs function of both activated megakaryocytes and malignant stem cells
- Megakaryocytes produce cytokines and growth factors that drive myelofibrosis



LSD1 inhibition reduces production of megakaryocytes, growth factors and cytokines = symptom improvement

Potential to extinguish self-renewal of malignant stem cells = potential to improve overall survival

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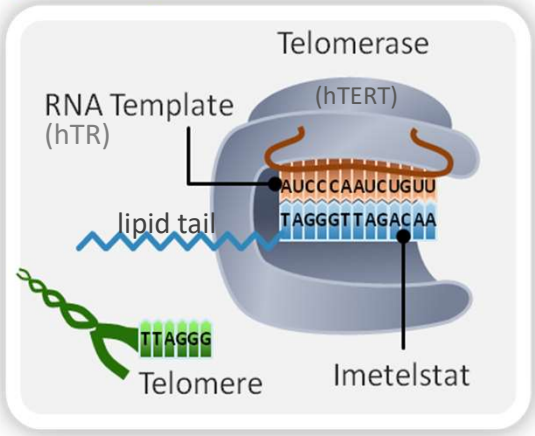
Imetelstat: First-in-Class Telomerase Inhibitor

Place video here

Imetelstat

- **Proprietary:** 13-mer thio-phosphoramidate oligonucleotide complementary to hTR, with covalently-bound lipid tail to increase cell permeability.
- **Potent, first in class competitive inhibitor of telomerase**: IC50 = 0.5-10 nM
- **Target:** selectively targets heme (MF) malignant stem and progenitor cell proliferation.[1, 2]

Imetelstat binds to RNA template preventing maintenance of telomeres

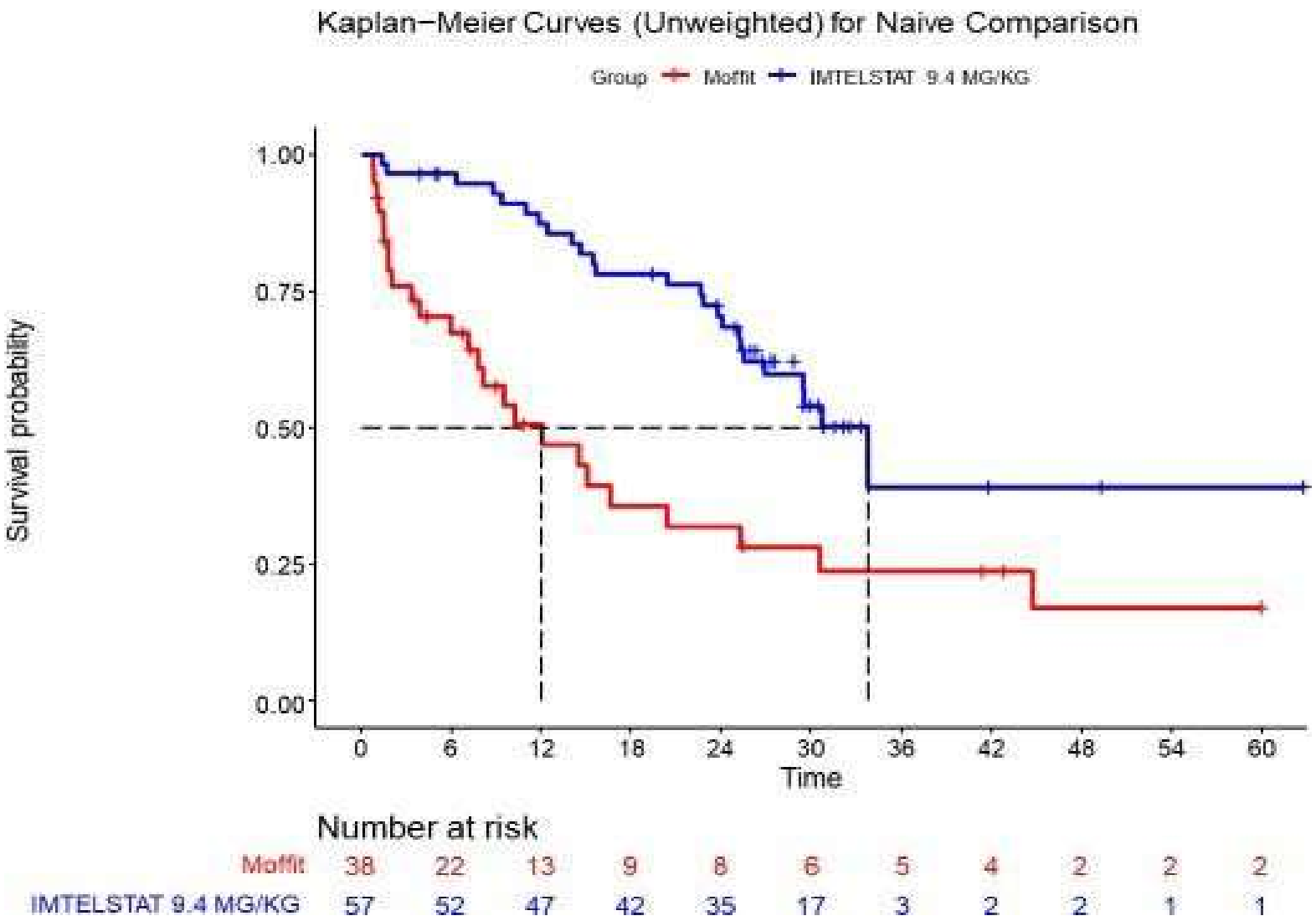


- Short telomere length (TL), high levels of telomerase activity (TA) and high expression of human telomerase reverse transcriptase (hTERT) correlated with higher risk, disease progression and shorter OS in patients with myeloid malignancies.[3-5]
- Nonclinical studies demonstrated that imetelstat reduces TA, hTERT expression level, and JAK2V617F^{+} hematopoietic progenitor cells in MF patient samples, indicative of mechanism based on-target activity.[1,2]
- **Cells with high levels of TA and hTERT and short TL, represent best target for treatment with telomerase inhibitor.**

[1]Wang, et al. *Blood Adv* 2018;2:2378-88.
[2]Mosoyan, et al. *Leukemia* 2017;31:2458-67.
[3]Briatore, et al. *Cancer Biol Ther* 2009;8:883-9.
[4]Kishtagari and Watts. *Ther Adv Hematol* 2017;8:317-26.
[5]Wang, et al. *Int J Lab Hematol* 2010;32:230-8.

IMbark Phase 2 Imetelstat Data: Survival[1]

ClincialTrials.gov (NCT02426086)



Median overall survival:

28.1 months (95% CI, 22.8 - 31.6)

After discontinuation of ruxolitinib[2-4]:

Median overall survival is ~14-16 months.

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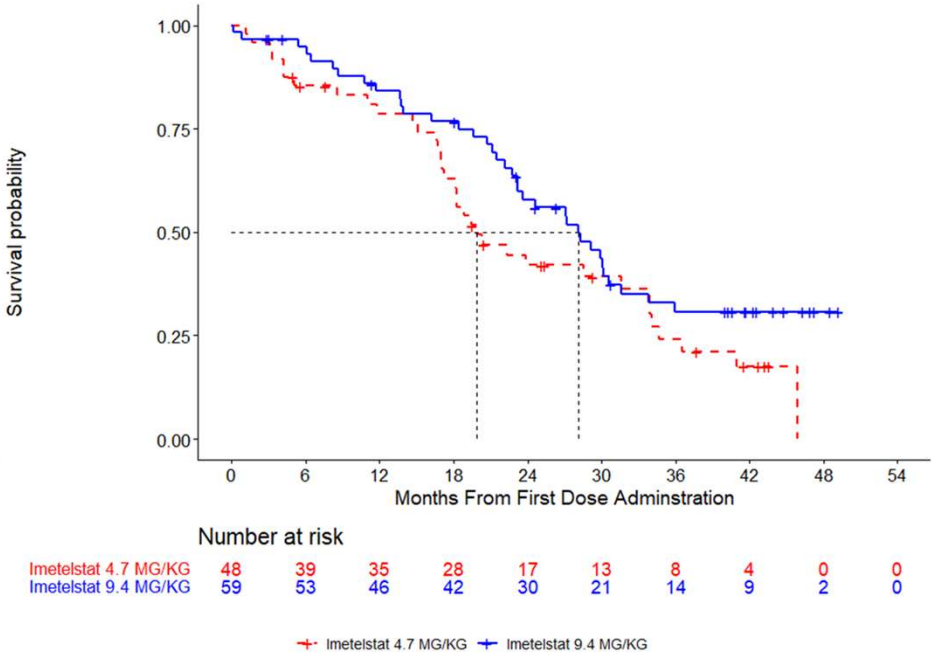
1. Mascarenhas J et al. EHA 2020. Abstract EP1107;
2. Kuykendall AT et al. *Ann Hematol.* 2018;97(3):435-441;
3. Newberry KJ et al. *Blood.* 2017;130(9):1125-1131;
4. Spiegel JY et al. *Blood Adv.* 2017;1(20):1729-1738.

Potential OS Improvement with 9.4 mg/kg Imetelstat Treatment in Patients with MF R/R to JAKi



	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Number of events, n (%)	35 (72.9%)	36 (61.0%)
Number censored, n (%)	13 (27.1%)	23 (39.0%)
Median Overall Survival (months) (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
12-months survival rate % (95% CI)	78.6 (63.9, 87.9)	84.0 (71.6, 91.4)
24-months survival rate % (95% CI)	42.0 (27.4, 56.0)	57.9 (43.6, 69.7)

OS analysis was performed based on database lock in April 2020; median follow-up was 41.7 months (range 0.2, 49.2)

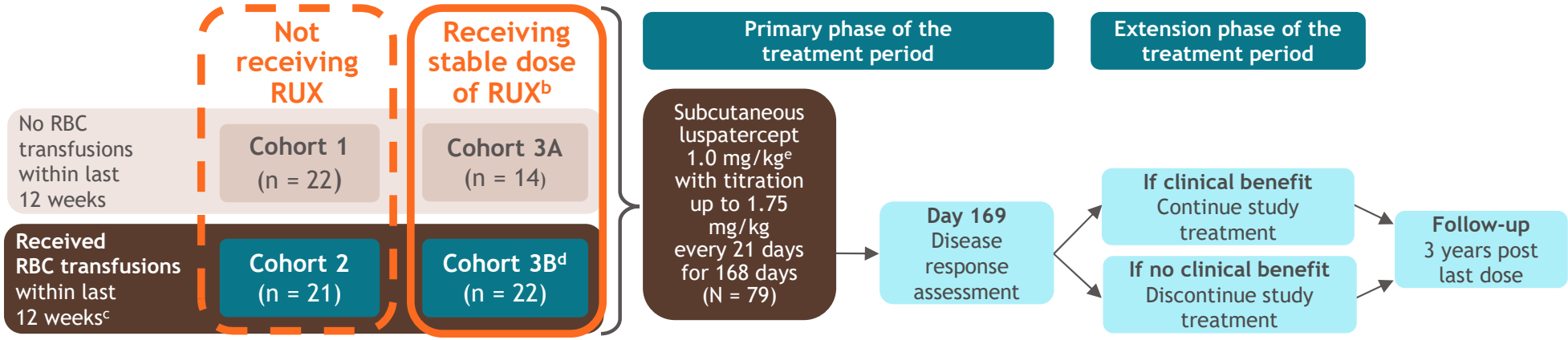
Similar results were observed when sensitivity analyses accounted for confounding factors of subsequent therapies, including hematopoietic stem cell transplantation and dose escalation from 4.7 mg/kg to 9.4 mg/kg

Mascarenhas et. al. ASH 2020

ACE-536-MF-001 study design

- This study reports the results of the ongoing open-label, phase 2 ACE-536-MF-001 trial evaluating luspatercept in subjects with MF and anemia, focusing on response in subjects requiring RBC transfusions (NCT03194542)

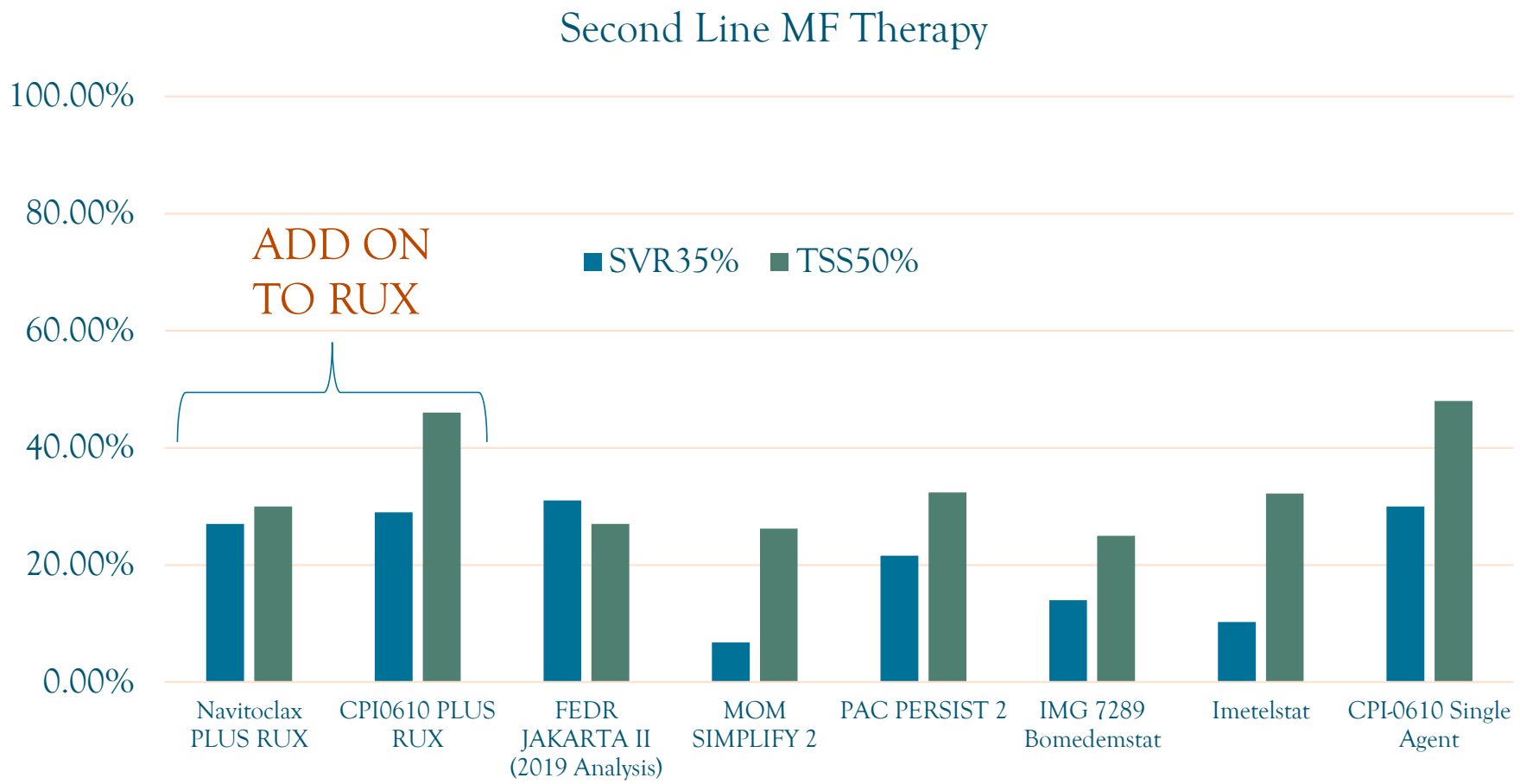
Figure 1. ACE-536-MF-001 study design[a]



- 79 subjects with MF and anemia had been enrolled by the data cutoff and were included in this updated analysis (March 29, 2020)
- The analyses presented here focus on response in subjects requiring RBC transfusions (Cohorts 2 and 3B); safety is reported for all 79 subjects on study

As of March 29, 2020, 16 (20%) subjects remain on treatment. [a]Enrolled subjects had primary or post-essential thrombocythemia/post-polycythemia vera myelofibrosis; [b]A stable daily dose of RUX for at least 16 weeks at enrollment; for the 3 subjects enrolled in the expansion cohort in Cohort 3B, subjects were receiving a stable RUX dose for 40 weeks; [c]6–12 RBC units/84 days prior to treatment; or 4–12 units/84 days for the 3 subjects enrolled in the expansion cohort in Cohort 3B; [d]Including 3 subjects enrolled in the expansion cohort; [e]The starting dose was 1.33 mg/kg in the expansion cohort subjects. MF, myelofibrosis; RBC, red blood cell; RUX, ruxolitinib.

Comparison for 2L Therapy



Pemmaraju et. al. ASH 2020
Verstovsek et. al. ASH 2020
Harrison et. al. ASH 2019
Verstovsek et. al.
Mascarenhas et. al.
Yacoub et. al. ASH 2020
Mascarenhas et. al. ASH 2020
Talpaz et. al ASH 2020

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New Drugs - MF

- Burden of Having MF
- JAK Inhibitors
- New Drugs Front Line
- New Drugs Second Line
- Future State

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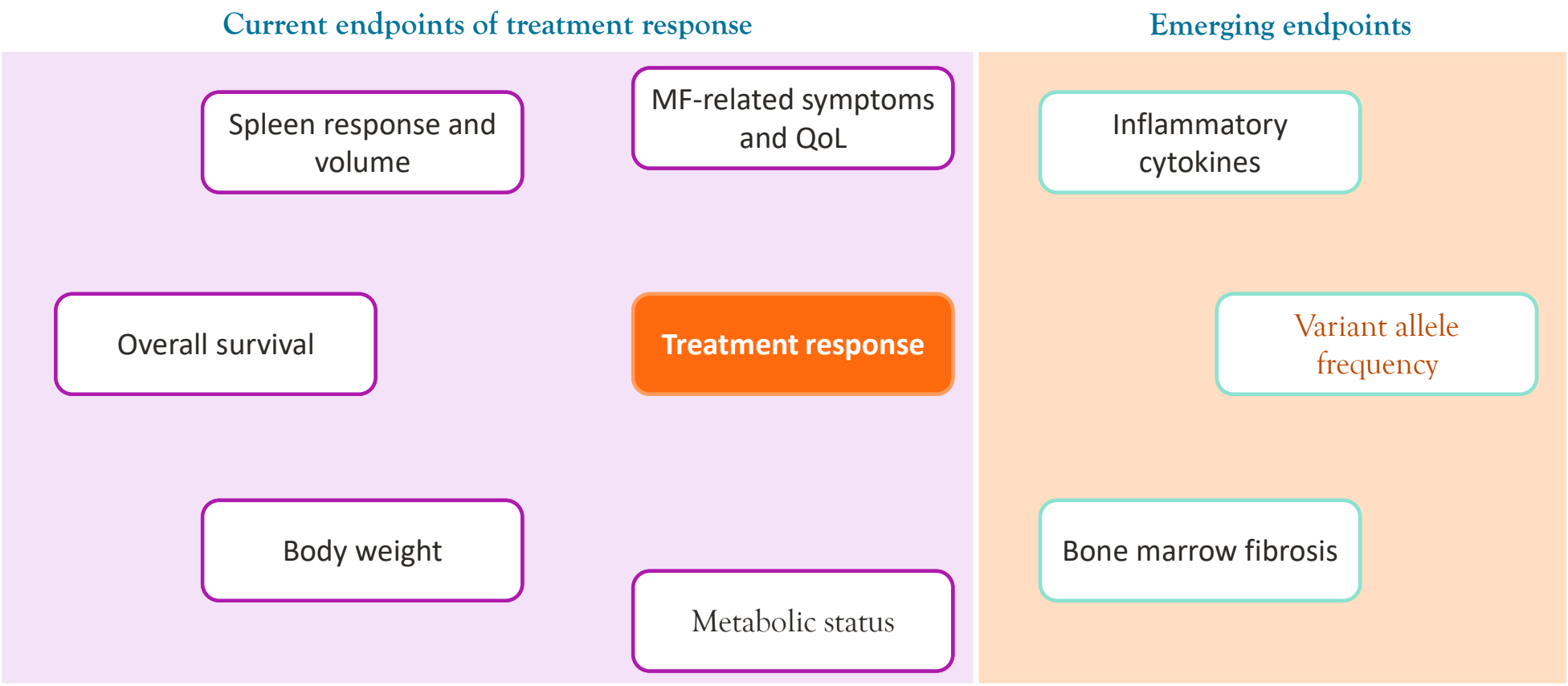
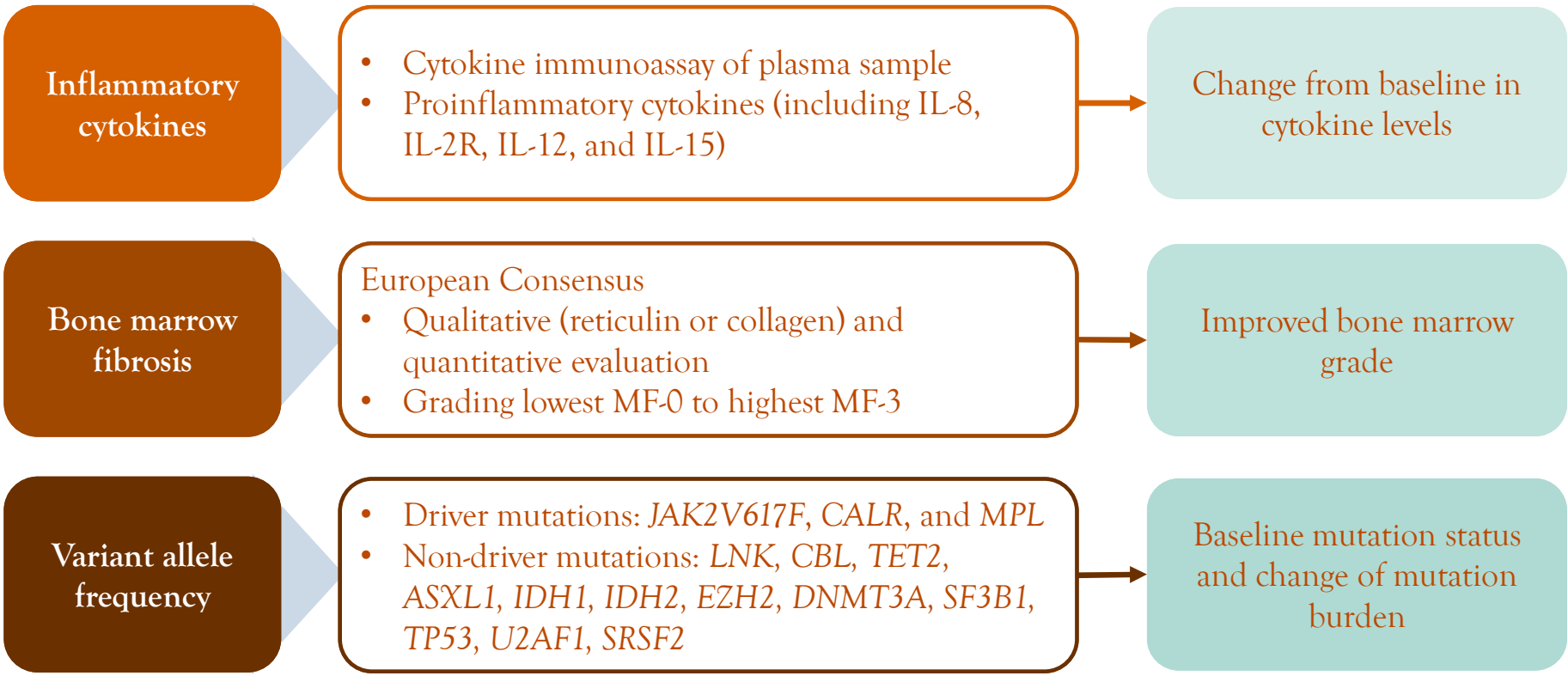
Measuring treatment response in MF



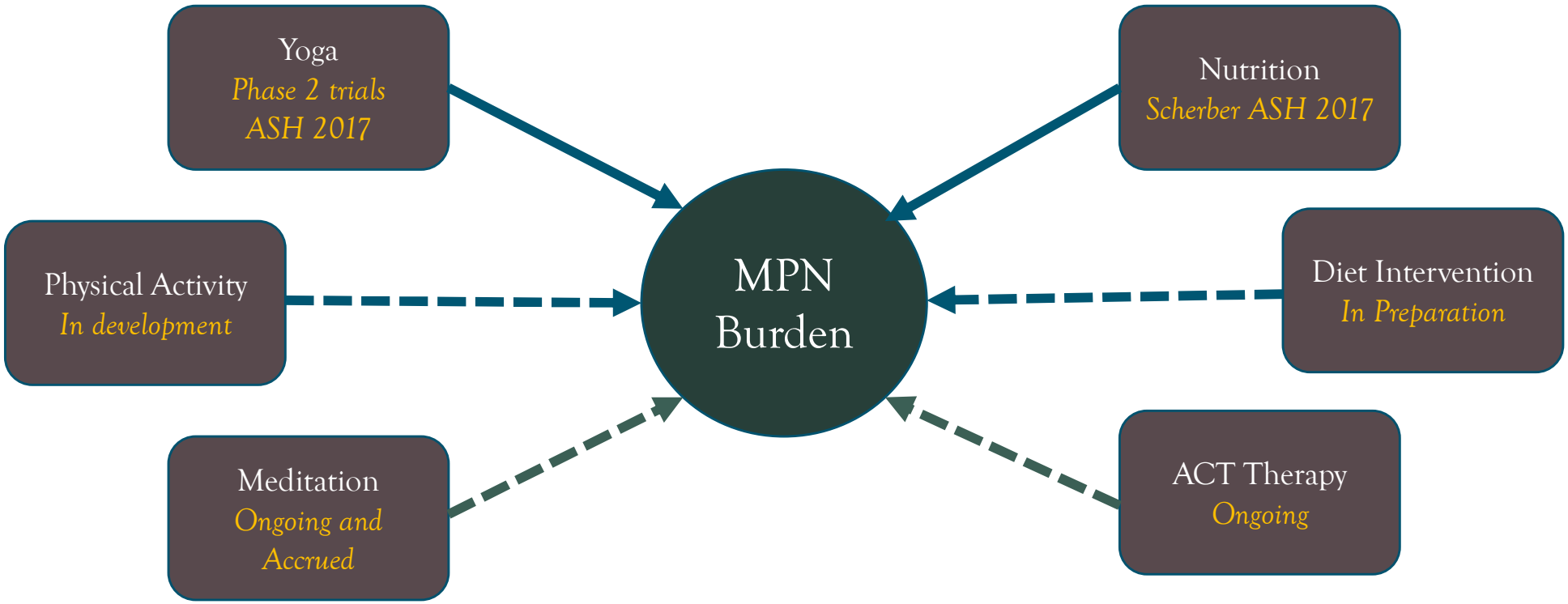
Savona MR. *Leukemia Res* 2014; **38**:1004–1012; Harrison CN. *Leukemia* 2016; **30**:1701–1707.

Endpoints assessing disease modification



Savona MR. *Leukemia Res* 2014; **38**:1004–1012; Harrison CN, *et al. Ann Hematol* 2020; **99**:1177–1119; Gianelli U, *et al. Mod Pathol* 2012; **25**:1193–1202; Tefferi A, *et al. J Clin Oncol* 2011; **29**:1356–1363.

Non Pharmacological Approaches for MPN Burden Relief



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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Myelofibrosis
NCCN Evidence Blocks™

NCCN Guidelines Index
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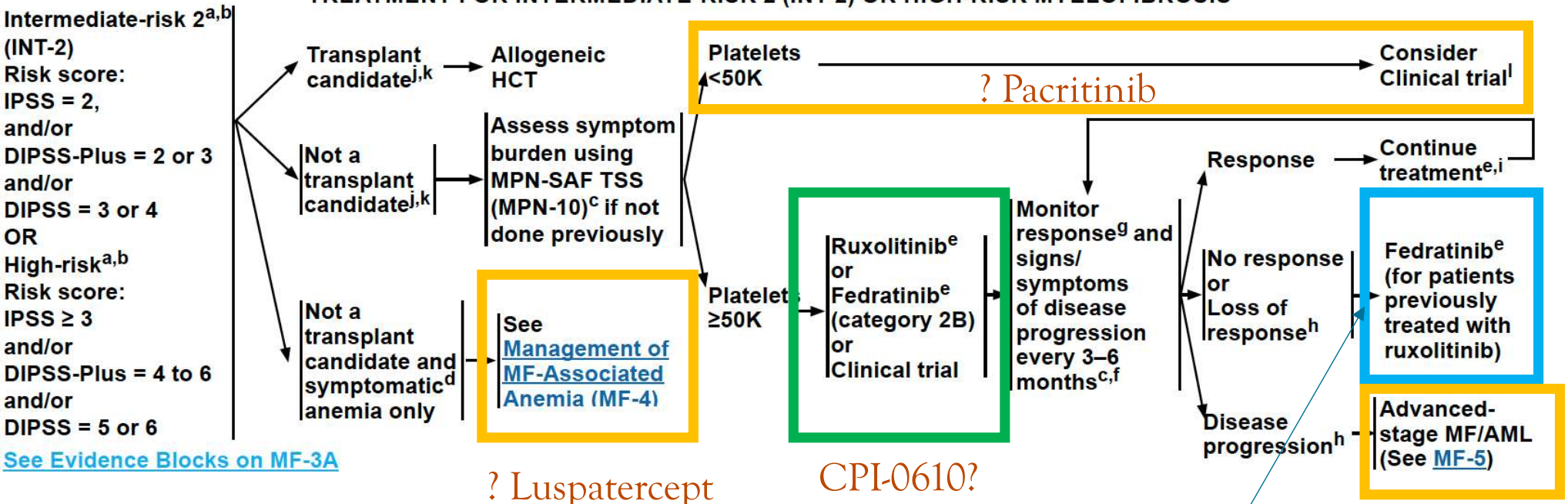
Discussion

TREATMENT FOR INTERMEDIATE-RISK 2 (INT-2) OR HIGH-RISK MYELOFIBROSIS



See Evidence Blocks on MF-3A

? Luspatercept
? Momelotinib
?CPI0610

CPI-0610?
Navitoclax?

Other JAKi
CPI0610
LSD7289
Rux Combo?

MPN QoL STUDY GROUP

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