Evolving Therapy of MPNs 2022

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Mays Cancer Center
UT Health San Antonio
MD Anderson Cancer Center

Disclosures

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

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

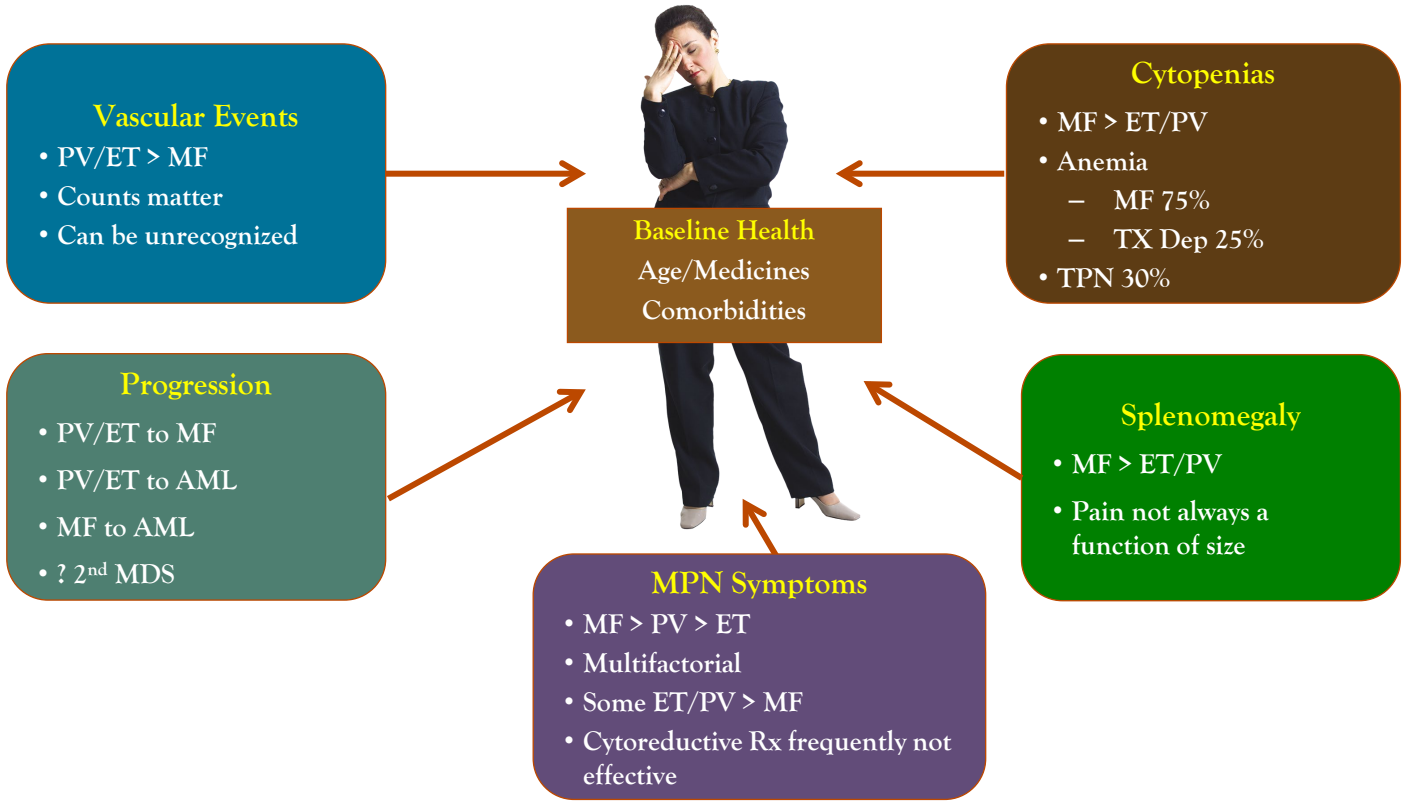
Off Label Use: Hydroxyurea, PEG Interferon, ruxolitinib

Therapy of MPNs 2022

- Goals and Targets
- ET and PV
- JAK Inhibitors as Foundation
- Non JAKi MOA
- Putting it all Together

Assessing MPN Burden

WHO Diagnosis Does Not Tell Whole Story



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American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide

Place Video Here

Phase 2 Study of the LSD1 Inhibitor IMG-7289 (Bomedemstat) for the Treatment of Essential Thrombocythemia (ET)

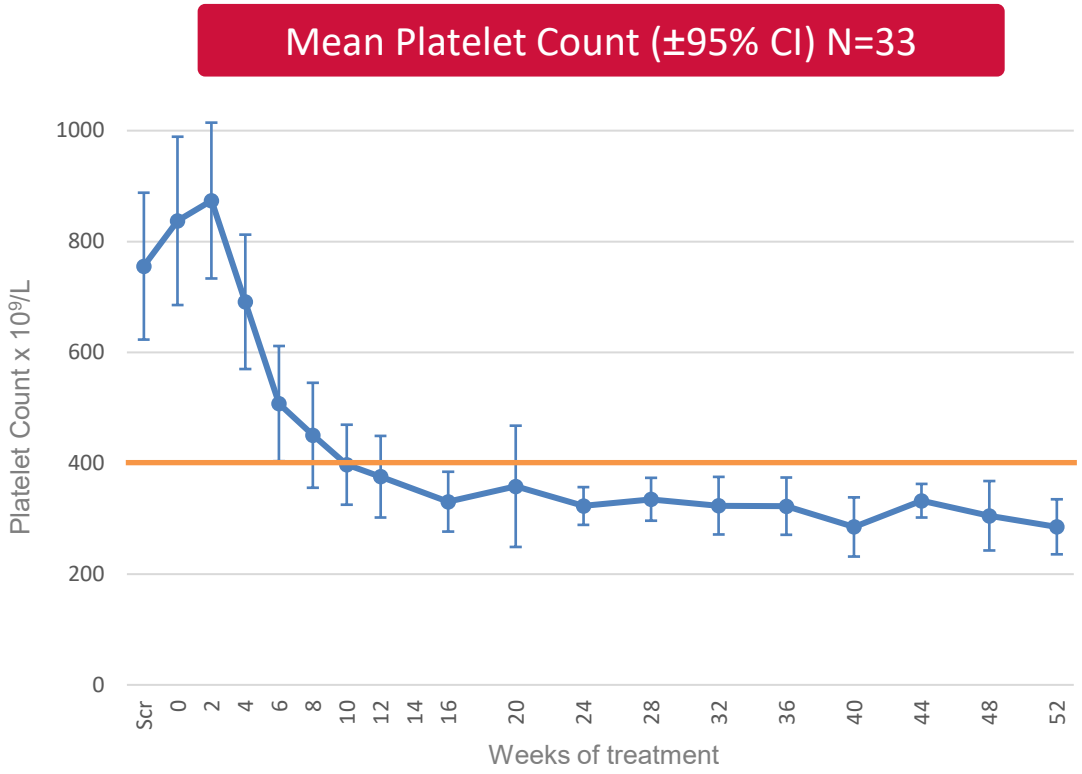
Francesca Palandri, MD, PhD[1*], David M Ross, MBBS, PhD, FRACP, FRCPA[4*], Tara Cochrane, MBBS, FRCPA, FRACP[5], Steven W Lane, MD, PhD[6], Stephen R Larsen, MBBS PhD FRACP FRCPA[7], Aaron T. Gerds, MD[8*], Anna B. Halpern, MD[9], Jake Shortt, FRACP, FRCPA, PhD[10], James M. Rossetti, DO[11], Kristen M. Pettit, MD[12], James Liang[20], Adam Mead, MBBChir[21], Monia Marchetti, MD[22], Alessandro Vannucchi, MD[23], Andrew Wilson, MD[24], Joachim R. Göthert, MD[25], Merit Hanna[26], Amber Jones, MA[13*], Jennifer Peppe, BA[14*], Georges Natsoulis, Ph.D.[15*], Willis Navarro, MD[16], Wan-Jen Hong, MD[16], William S. Stevenson, MBBS, PhD[17], Claire N. Harrison, DM[18], Moshe Talpaz, MD[12], Nicola Vianelli, MD[2,3], and Hugh Young Rienhoff Jr., MD[19]

[1]Institute of Hematology "L. & A. Seràgnoli", Sant'Orsola-Malpighi University Hospital, Bologna, Italy; [2]Azienda Ospedaliero-Universitaria S.Orsola-Malpighi di Bologna, Bologna, Italy; [3]Institute of Hematology "L. & A. Seragnoli", Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni 15, Bologna, Italy; [4]Department of Haematology, Royal Adelaide Hospital and SA Pathology, Adelaide, SA, Australia; [5]Department of Haematology, Gold Coast University Hospital, Southport, Australia; [6]QIMR Berghofer Medical Research Institute, Brisbane, Australia; [7]Institute of Haematology, Royal Prince Alfred Hospital, Sydney, NSW, Australia; [8]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [9]Department of Medicine, Division of Hematology, University of Washington, Seattle, WA; [10]Monash Haematology, Monash Health, Clayton, VIC, Australia; [11]UPMC Hillman Cancer Center, Pittsburgh, PA; [12]Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI; [13]Imago Biosciences Inc., Chilton Polden, GBR; [14]Imago BioSciences, Inc., San Carlos, CA; [15]Imago Biosciences, Inc., San Carlos, CA; [16]Imago BioSciences, San Carlos, CA; [17]Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney, Australia; [18]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [19]Imago Biosciences, San Francisco; [20]Middlemore Clinical Trials, Auckland, New Zealand; [21]MRC Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom; [22]Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [23]University of Florence, AOU Careggi, CRIMM, Center for Research and Innovation of Myeloproliferative Neoplasms, Italy, Florence, Italy; [24]University College Hospital, NHS Foundation Trust, London, United Kingdom; [25]Department of Hematology, West German Cancer Center (WTZ), University Hospital Essen, Essen, Germany; [26]North Shore Hospital. Waitemata District Health Board, Auckland, New Zealand.

Abstract #386: Bomedemstat in ET

Primary Objective: Reduction in Platelet Count

Place Video Here



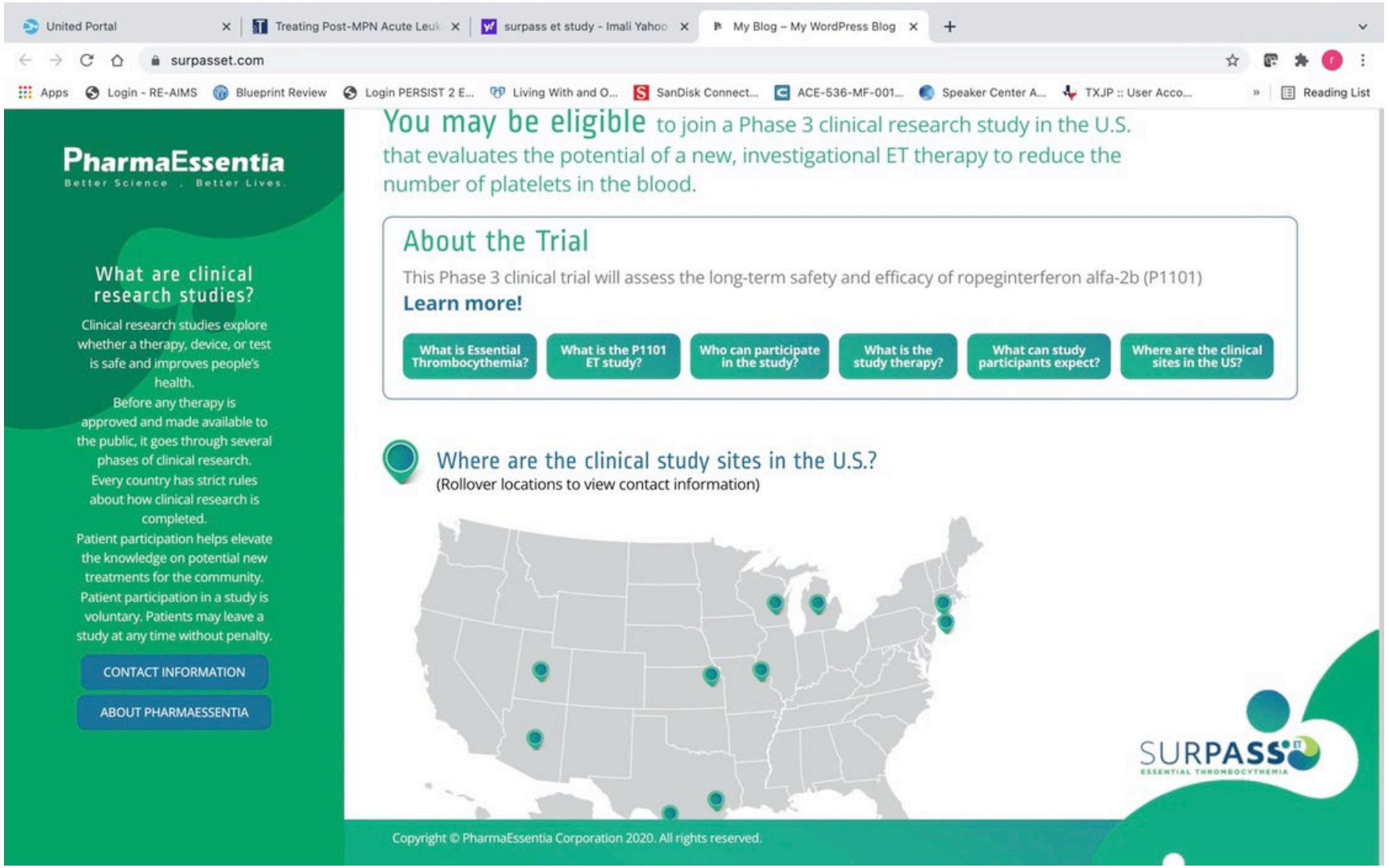
In the 29 patients treated for >6 weeks:

- 100% patients experienced a reduction in platelets
- 93% of patients achieved a platelet count of ≤400 x 10^9/L
- Response Rate*: 90% (26/29)

*Platelet count ≤400 x 10^9/L without thromboembolic events

Data cut-off date: 01 Nov 2021

SURPASS ET Study: 2L for ET NCT 04285086 (Clinicaltrials.GOV)



SurpassET.com

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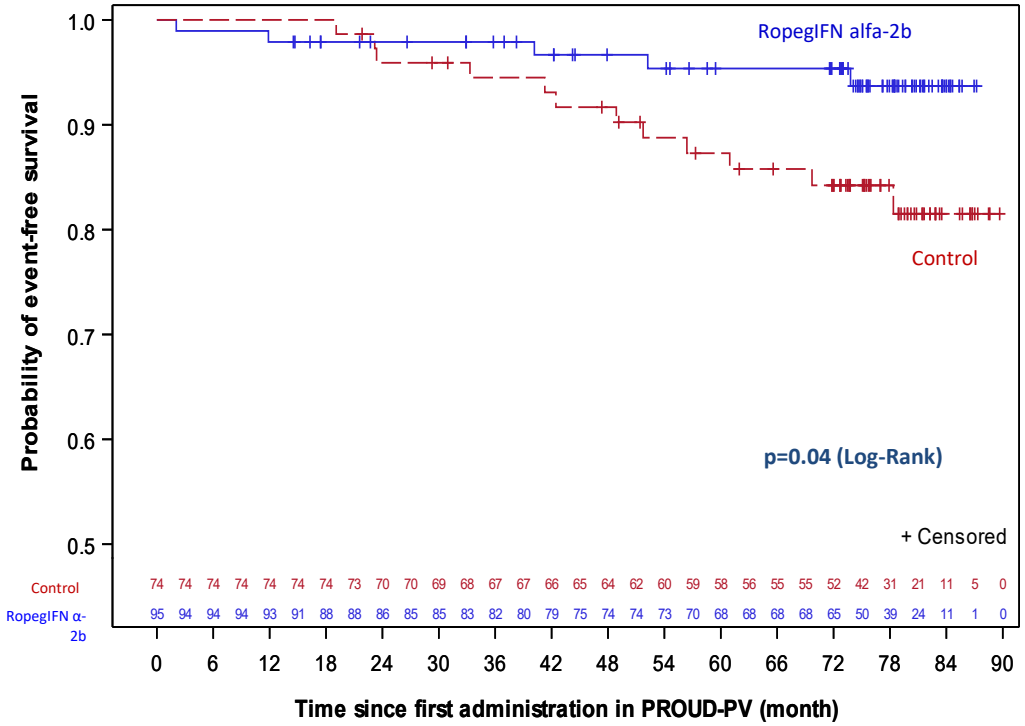
EHA EUROPEAN HEMATOLOGY ASSOCIATION
EHA2022 HYBRID VIRTUAL

ROPEGINTERFERON ALFA-2B ACHIEVES PATIENT-SPECIFIC TREATMENT GOALS IN POLYCYTHEMIA VERA: FINAL RESULTS FROM THE PROUD-PV/CONTINUATION-PV STUDIES

Heinz Gisslinger, MD, Christoph Klade, PhD, Pencho Georgiev, MD, Dorota Krochmalczyk, MD, Liana Gercheva-Kyuchukova, MD, Miklos Egyed, MD, Petr Dulicek, MD, Arpad Illes, MD, Halyna Pylypenko, MD, Lylia Sivcheva, MD, Jiří Mayer, MD, Vera Yablokova, MD, Kurt Krejcy, MD, Victoria Empson, MSc, Hans C. Hasselbalch, MD, Robert Kralovics, PhD and Jean-Jacques Kiladjian, MD PhD, for the PROUD-PV Study Group

Event-free survival

Risk events: death, disease progression and thromboembolic events

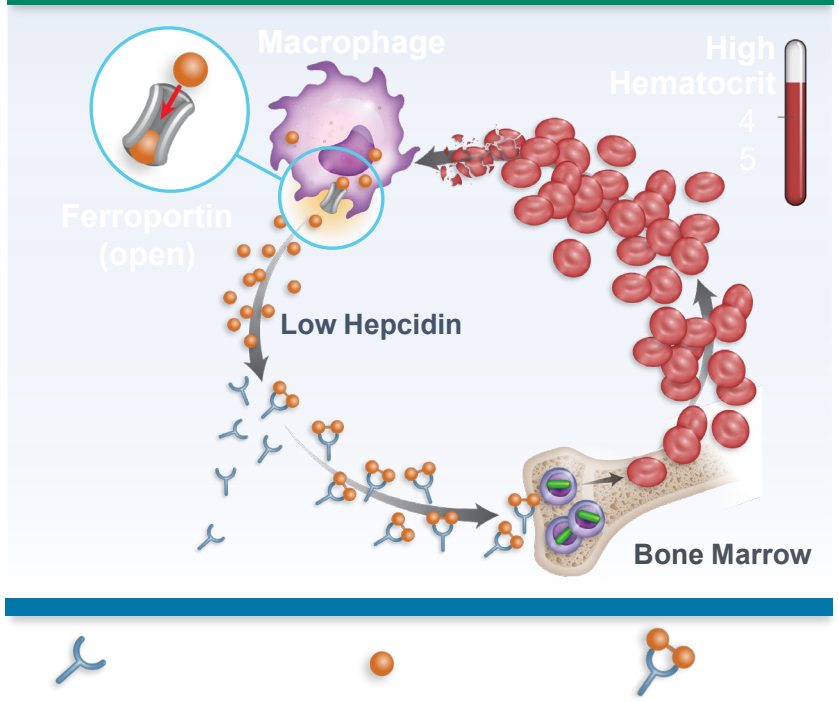


The probability of event-free survival was significantly higher among patients treated with ropeginterferon alfa-2b compared to the control arm (maximum treatment period 7.3 years)

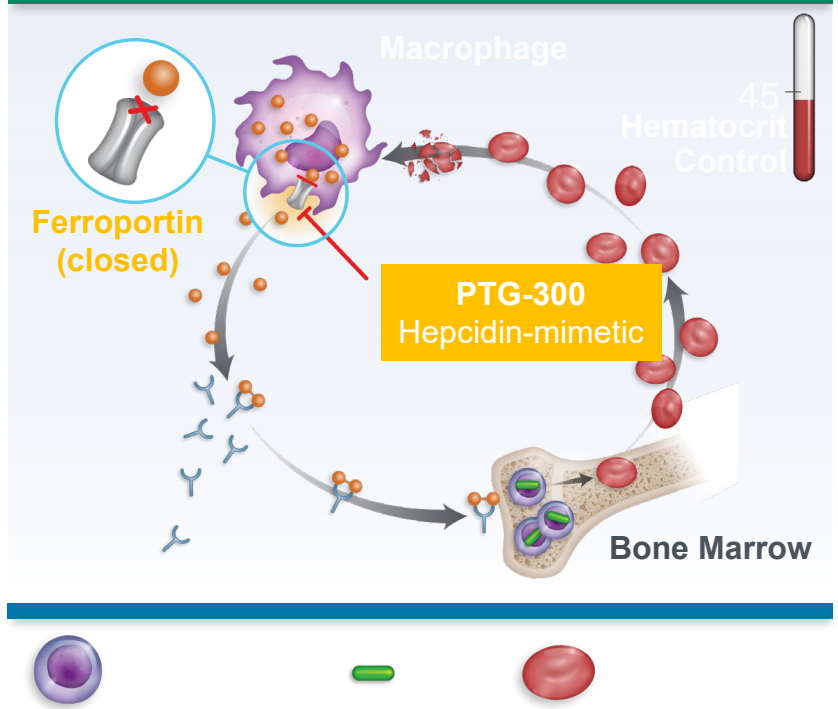
Rusfertide (PTG-300) Treatment in Phlebotomy-Dependent Polycythemia Vera

The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York; Protagonist Therapeutics, Newark, CA

Erythropoiesis in Polycythemia Vera



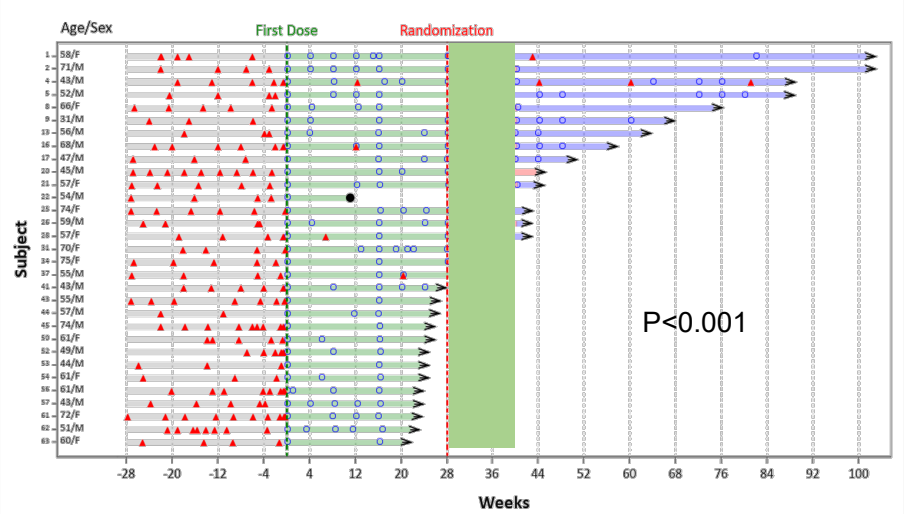
PTG-300 Suppresses PV Erythropoiesis



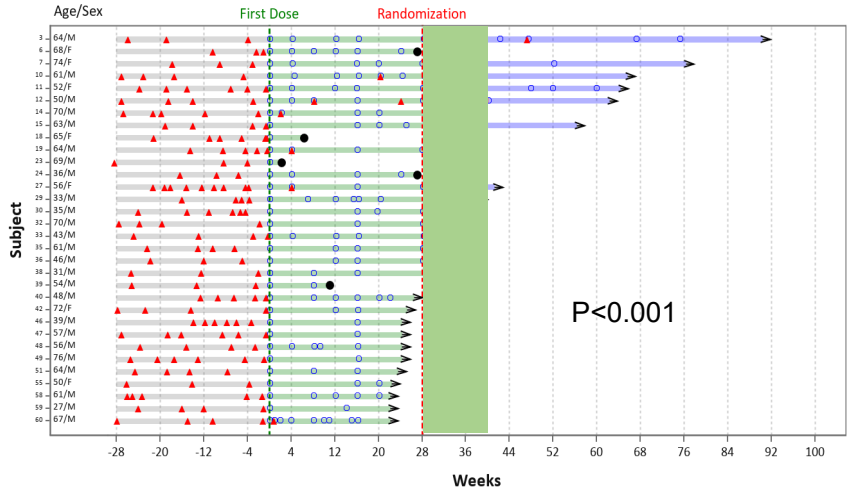
PRESENTED BY:
Ron Hoffman. Abstract # 7003

Effect of Rusfertide on Reducing Phlebotomy Frequency

PHLEBOTOMY ONLY (N=31, 49%)



PHLEBOTOMY + CYTOREDUCTIVE (N=32, 51%)



Median Dose 40-60 mg/week

During the first 28 weeks of treatment, **84% of patients did not require a phlebotomy,** 14% required one and 2% required two phlebotomies.

Data cut off Sept 30, 2021

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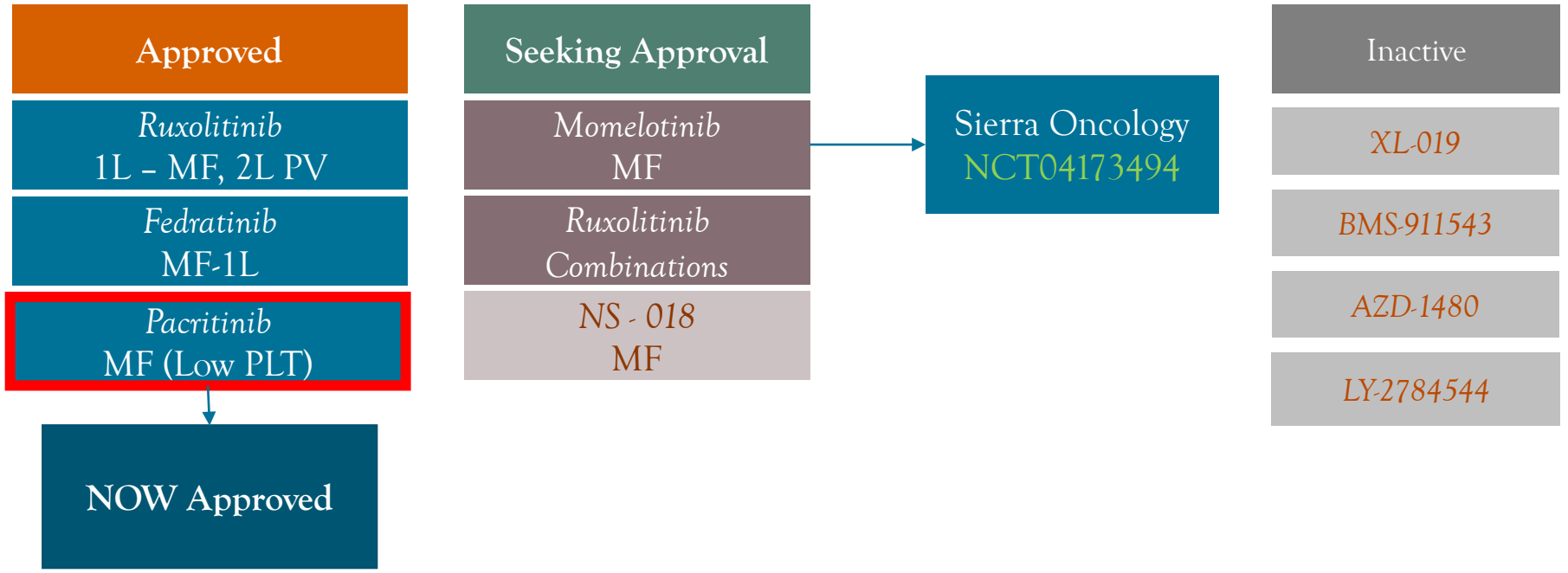
JAK Inhibitor Landscape 2022



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Ruxolitinib FDA Approved (MF)
November 16,2011

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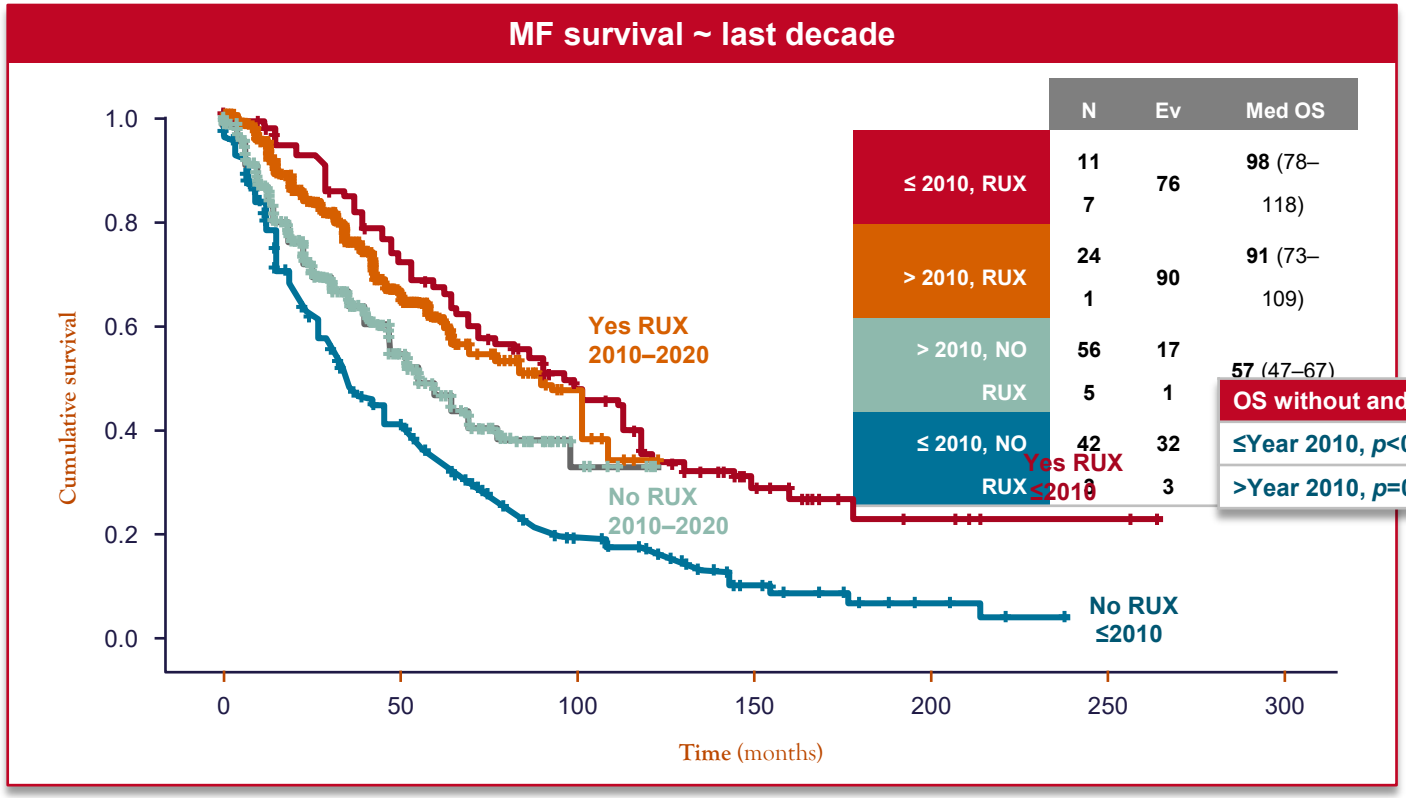
Results: OS ~ ruxolitinib



CI, confidence interval; Ev, event; HR, hazard ratio; MF, myelofibrosis; OS, overall survival; RUX, ruxolitinib.
Masarova L et. al. *ASH Annual Meeting and Exposition*. Abstract 2995. December 5–8 2020.

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Fedratinib FDA Approved (MF)
August 16,2019

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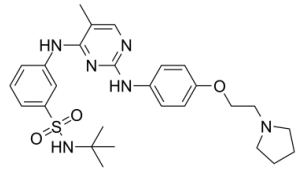
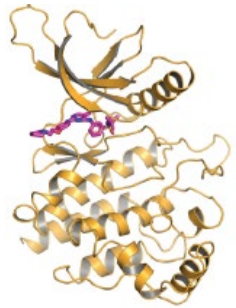
Fedratinib

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

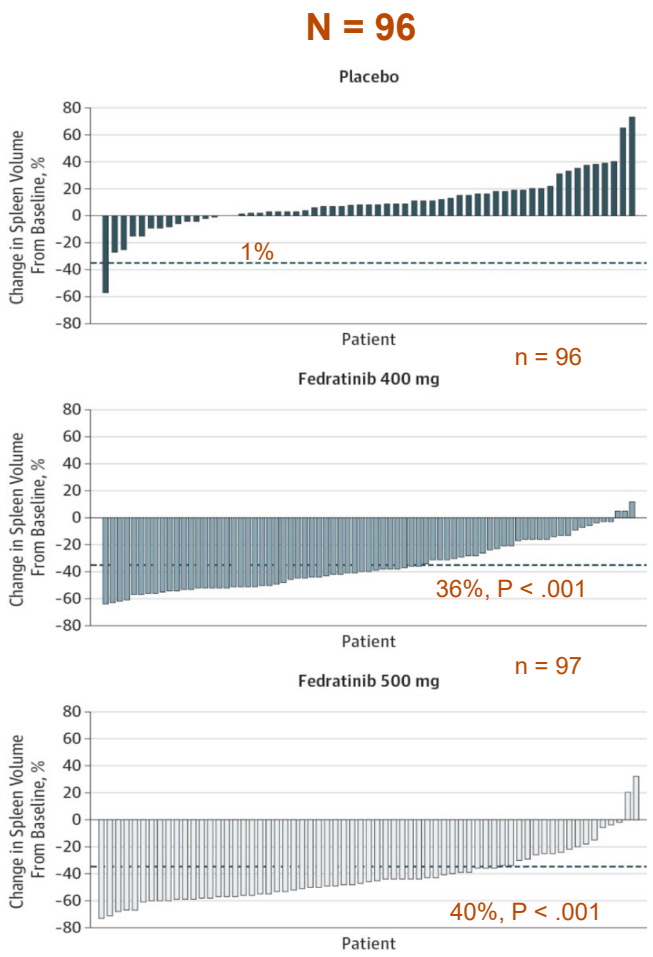


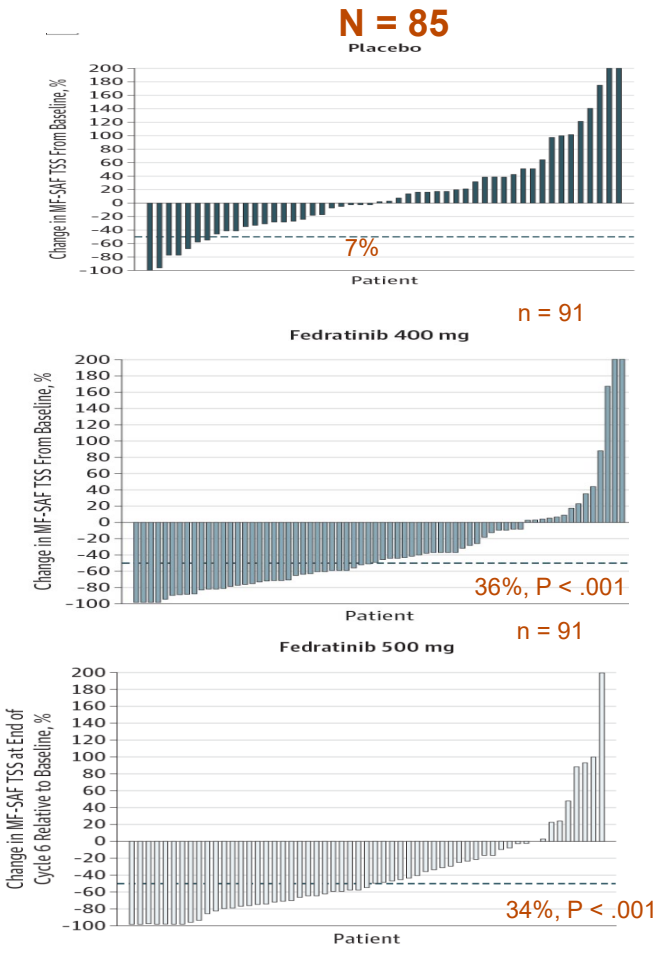
JAK2 KINASE DOMAIN – Fedratinib Complex[7]

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.

JAKARTA-1

Endpoints





Pardanani A, et al. JAMA Oncol. 2015;1:643-651.

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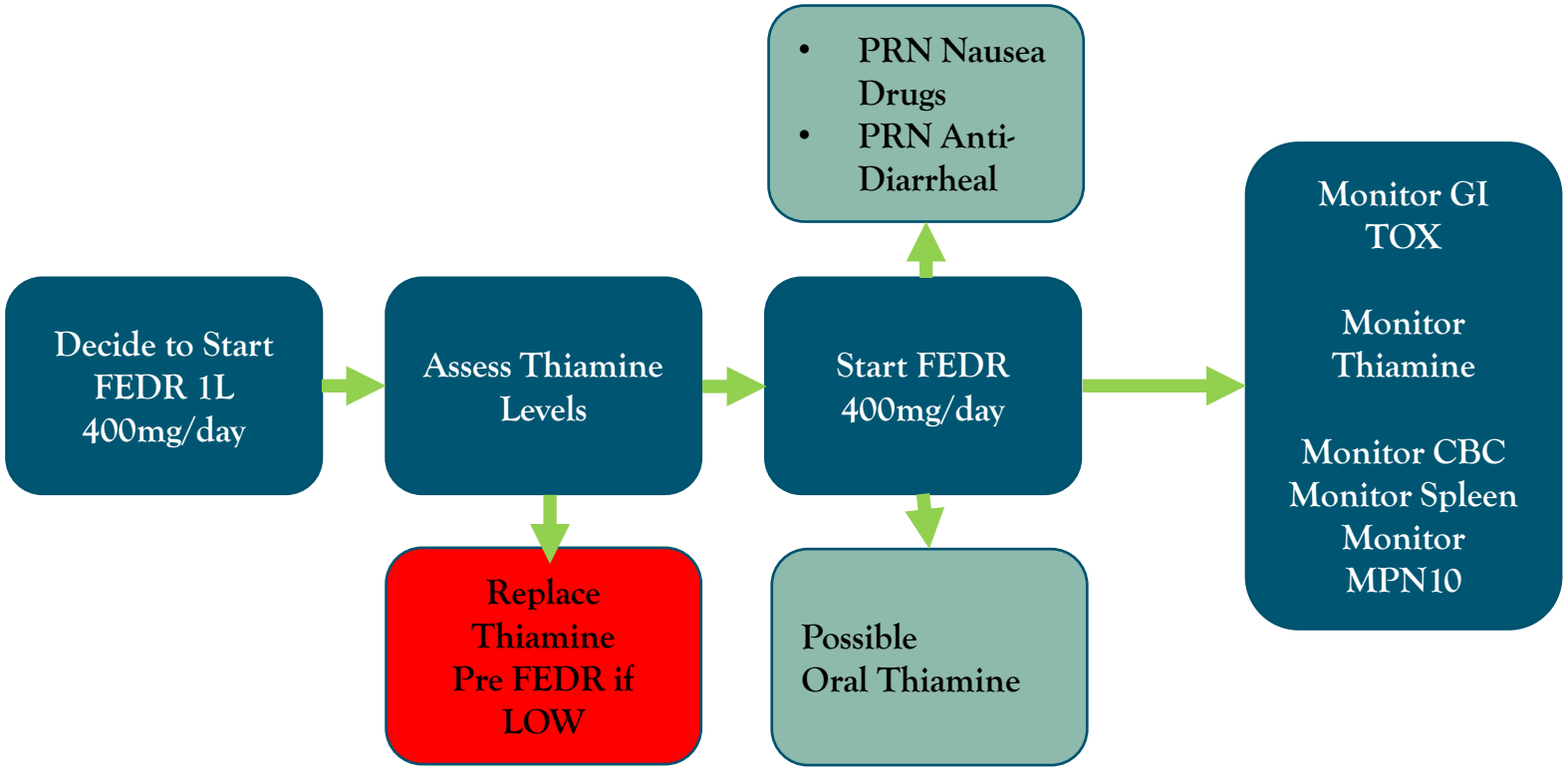
Using FEDR in MF Front Line



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Pacritinib FDA Approved (MF)
February 28th, 2022

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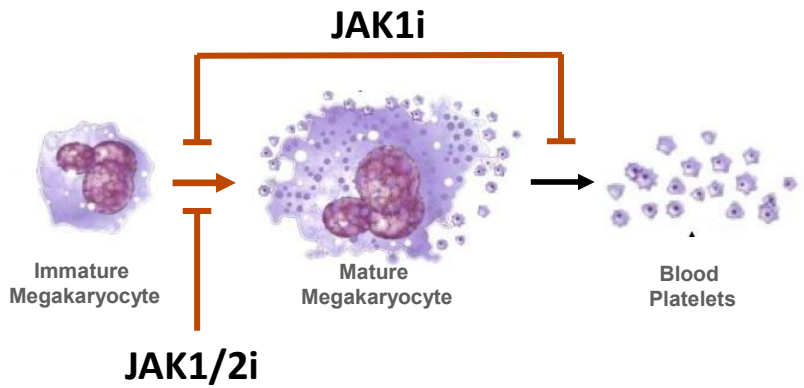
Pacritinib (PAC): A Selective Inhibitor of *JAK2* and IRAK1



- 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.

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

Non-Tyrosine Kinases of Interest IC_{50} (nM)

Kinase	Pacritinib	Ruxolitinib	Fedratinib
CSF1R	39.5	>3000	220
IRAK1	13.6	290	620

- **Only pacritinib is a potent inhibitor of IRAK1**

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.

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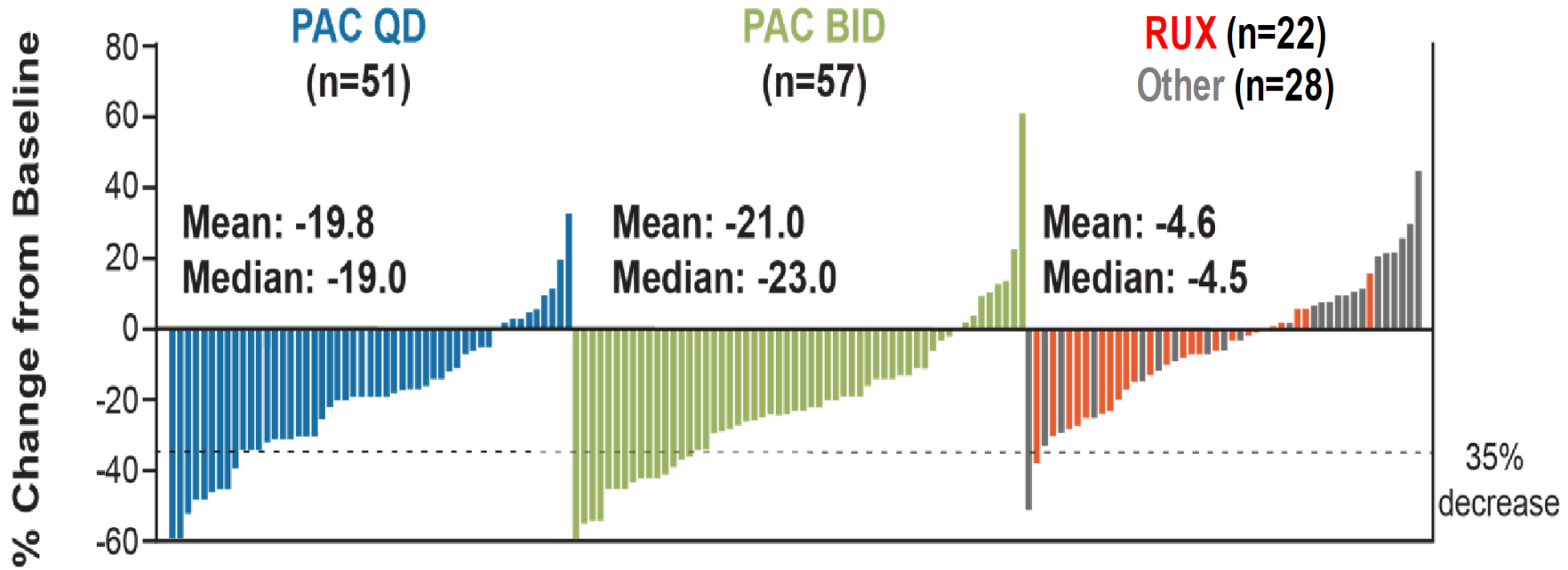
PERSIST-2

≥ 35% SVR



BID, twice daily; QD, daily.

Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659.

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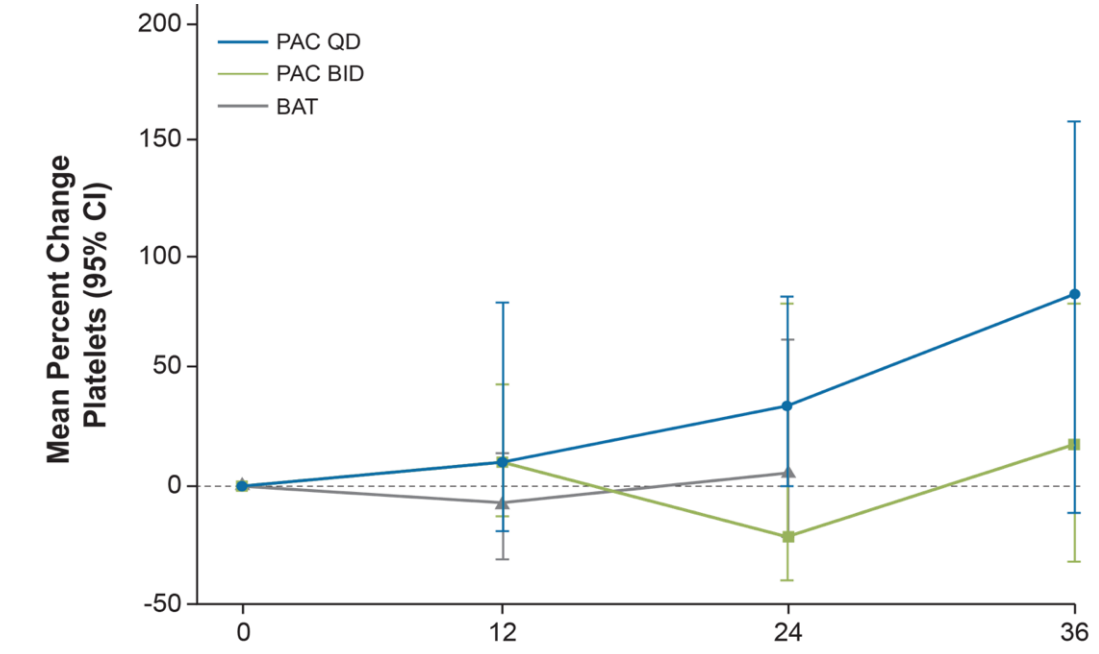
PERSIST-2 Percent Change in PLT Count

*BL PLT Count < 50,000/μL**

***Based on central laboratory values.**



Paitents at Risk				
PAC QD	50	28	19	10
PAC BID	47	32	16	11
BAT	42	23	12	

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Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659.

Momelotinib
Seeking Approval

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

2022 ASCO® ANNUAL MEETING

MOMENTUM: Phase 3 Randomized Study of Momelotinib (MMB) versus Danazol (DAN) in Symptomatic and Anemic Myelofibrosis (MF) Patients Previously Treated with a JAK Inhibitor

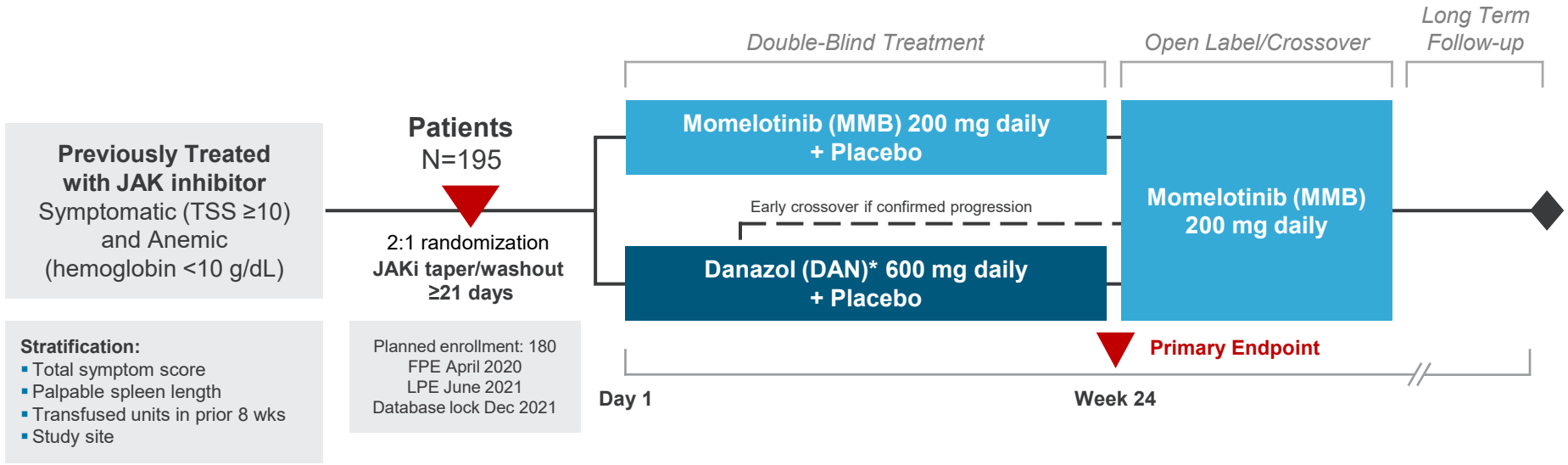
Ruben Mesa[1], Aaron T. Gerds[2], Alessandro Vannucchi[3], Haifa Kathrin Al-Ali[4], David Lavie[5], Andrew Kuykendall[6], Sebastian Grosicki[7], Alessandra Iurlo[8], Yeow Tee Goh[9], Mihaela Lazaroiu[10], Miklos Egyed[11], Maria Laura Fox[12], Donal McLornan[13], Andrew Perkins[14], Sung-Soo Yoon[15], Vikas Gupta[16], Jean-Jacques Kiladjian[17], Rafe Donahue[18], Jun Kawashima[18], Srdan Verstovsek[19]

[1]Mays Cancer Center at UT Health San Antonio MD Anderson, San Antonio, TX; [2]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [3]University of Florence and AOU Careggi, Florence, Italy; [4]University Hospital of Halle, Halle, Germany; [5]Hadassah-Hebrew University Medical Center, Jerusalem, Israel; [6]Moffitt Cancer Center, Tampa, FL; [7]Medical University of Silesia, Katowice, Poland; [8]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [9]Singapore General Hospital, Singapore; [10]Policlinica de Diagnostic Rapid Brasov, Romania; [11]Somogy County Mór Kaposi General Hospital, Kaposvár, Hungary; [12]Vall d'Hebron Institute of Oncology, University Hospital Vall d'Hebron, Barcelona, Spain; [13]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [14]Monash University, Melbourne, Australia; [15]Seoul National University Hospital, Seoul, South Korea; [16]Princess Margaret Cancer Centre, Toronto, Ontario; [17]Université de Paris, AP-HP, Hôpital Saint-Louis, Centre d'Investigations Cliniques, INSERM, CIC1427, Paris, France; [18]Sierra Oncology Inc., San Mateo, CA; [19]The University of Texas MD Anderson Cancer Center, Houston, TX

PRESENTED BY:

Ruben Mesa, MD, FACP
Director, Mays Cancer Center at UT Health San Antonio MD Anderson

MOMENTUM Study Design



Primary Endpoint

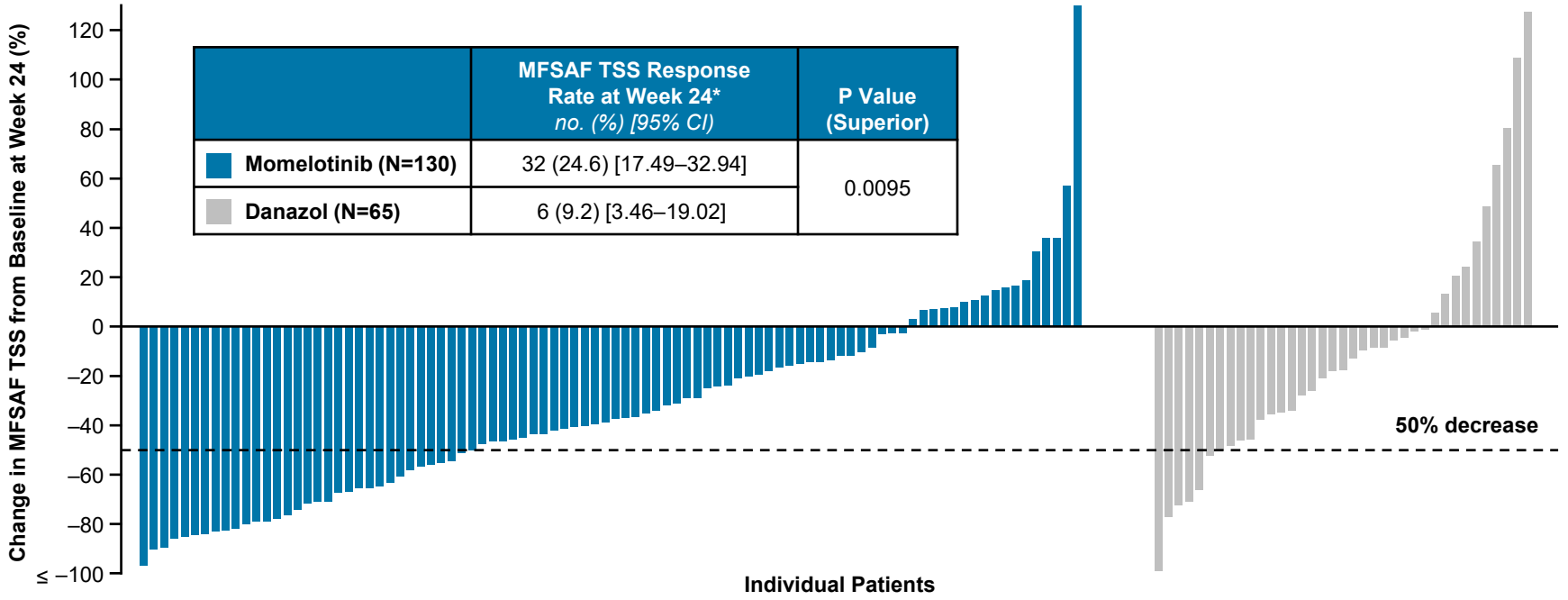
- Total symptom score (TSS) response rate at Week 24

Key Secondary Endpoints

- Transfusion independence (TI) rate at Week 24
- Splenic response rate (SRR) at Week 24

ClinicalTrials.gov: **NCT04173494**
*Danazol was selected as an appropriate comparator given its use to ameliorate anemia in MF patients, as recommended by NCCN, ESMO guidelines.
TSS response defined as achieving ≥50% reduction in TSS over the 28 days immediately prior to the end of week 24 compared to baseline.
TI defined as not requiring red blood cell transfusion in the last 12 weeks of the 24-week randomized period, with all hemoglobin levels during the 12-week interval of ≥8 g/dL.
SRR defined as achieving a **≥25%** or **≥35%** reduction in spleen volume from baseline.

MFSAF Total Symptom Score Response Rate* at W24



*Defined as the proportion of patients who achieve ≥50% reduction in TSS over the 28 days immediately prior to the end of Week 24 compared to baseline.

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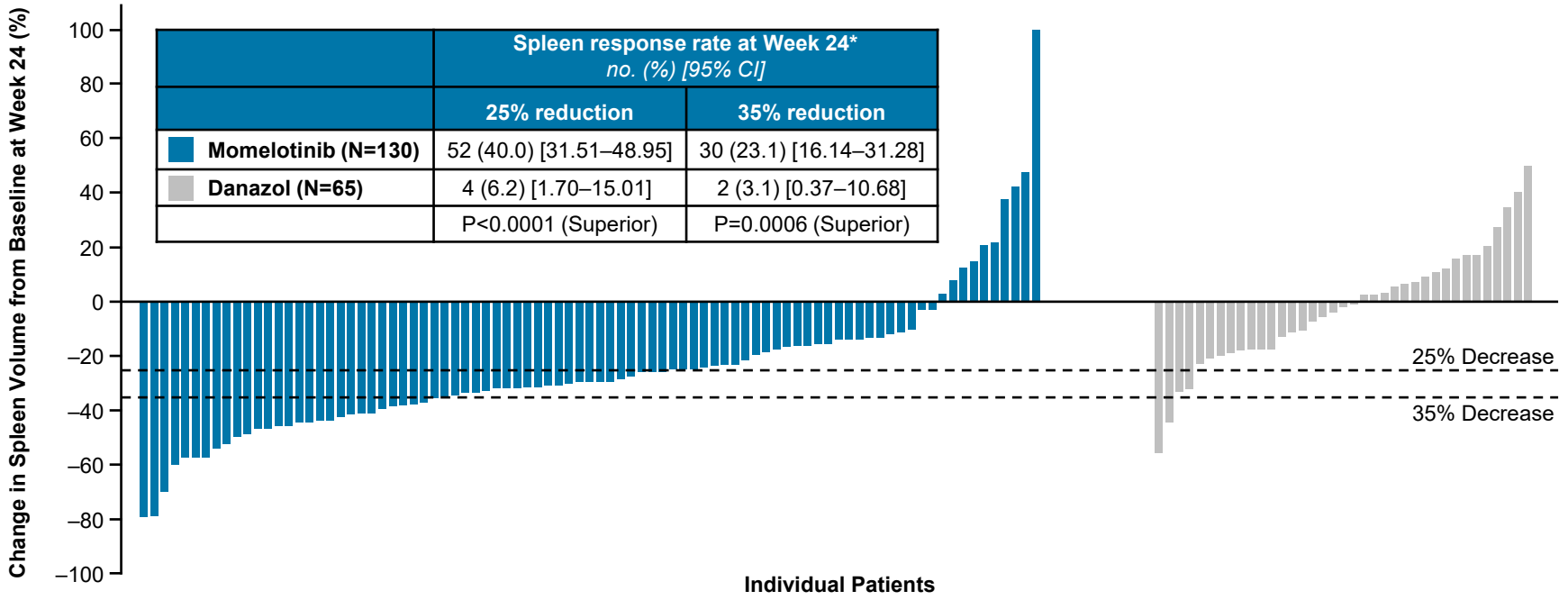
Spleen Response Rate* at Week 24



*Defined as the proportion of patients who have a reduction in spleen volume of ≥25% or ≥35% from baseline.

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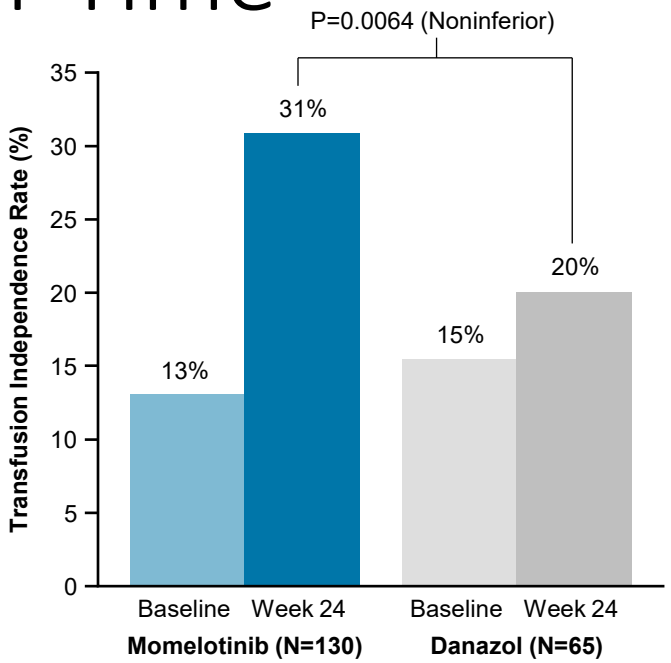
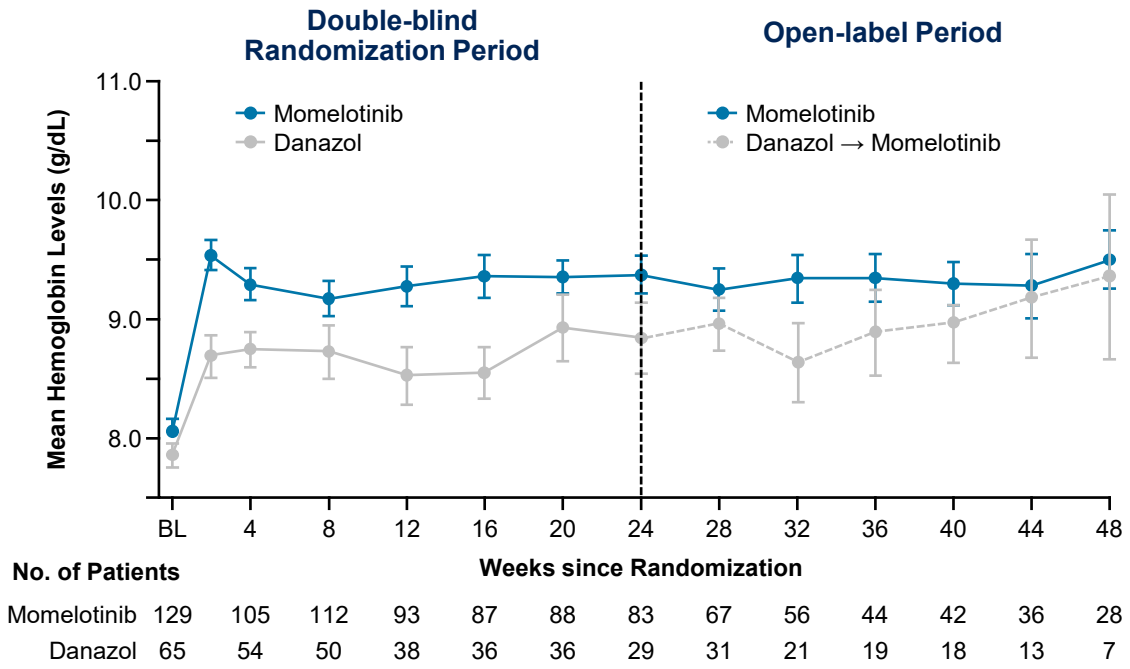
Transfusion Independence* Rate at W24 and Mean Hemoglobin Over Time





*Defined as not requiring red blood cell transfusion in the terminal 12 weeks of the 24-week randomized period, with all hemoglobin levels during the 12-week interval of ≥8 g/dL.

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Ruben Mesa, MD, FACP
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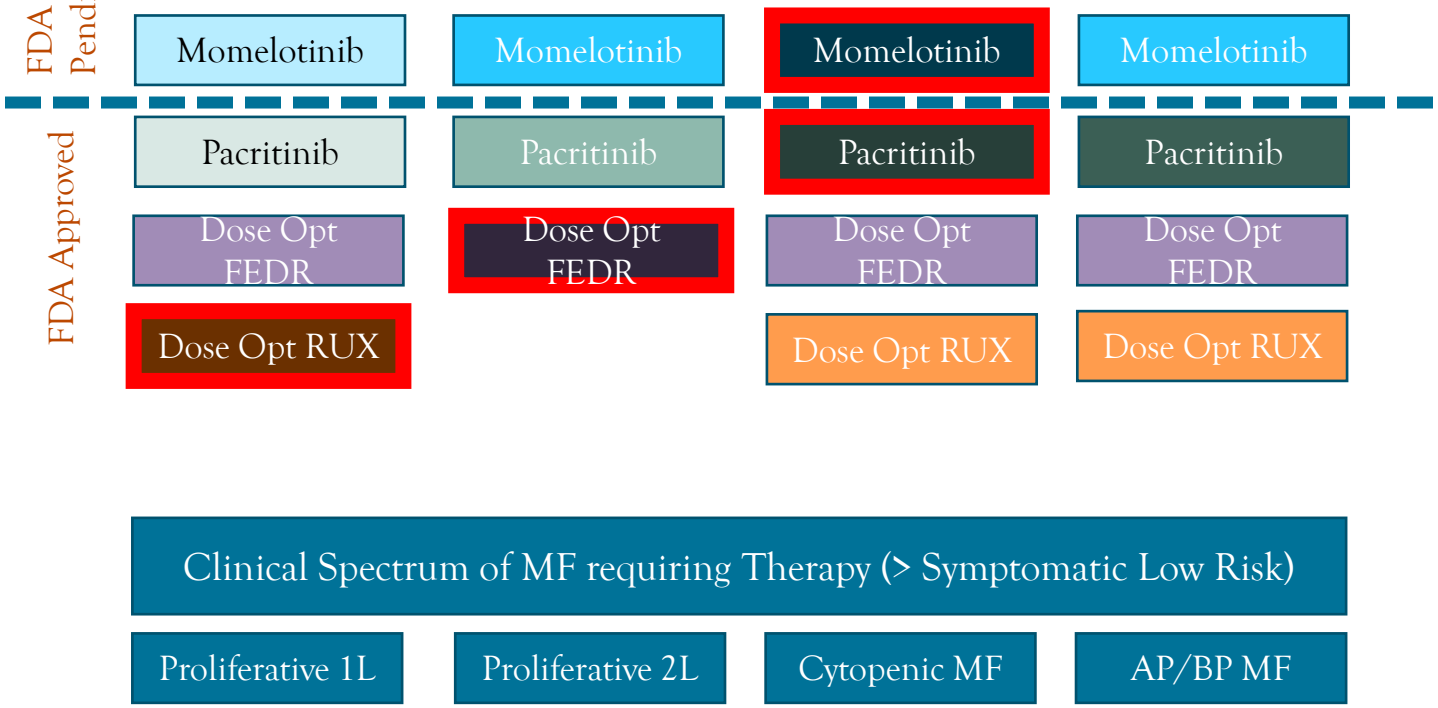
Step 1 for MF Management: Optimize JAK Inhibition



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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

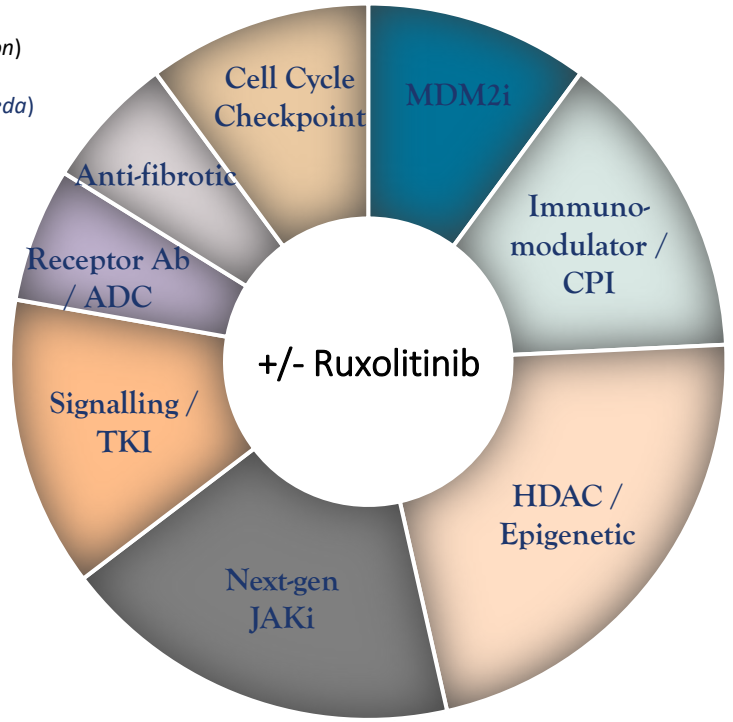
- P2 SL-401 | CD123-toxin (*Stemline*)

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

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BET Inhibitor Pelabresib (CPI-0610) Combined With Ruxolitinib in Patients With Myelofibrosis — JAK Inhibitor-Naïve or With Suboptimal Response to Ruxolitinib

Preliminary Data From the MANIFEST Study

John Mascarenhas,[1] Marina Kremyanskaya,[1] Andrea Patriarca,[2] **Claire Harrison**,[3] Prithviraj Bose,[4] Raajit K Rampal,[5] Francesca Palandri,[6] Timothy Devos,[7] Francesco Passamonti,[8] Gabriela Hobbs,[9] Moshe Talpaz,[10] Alessandro Vannucchi,[11] Jean-Jacques Kiladjian,[12] Srdan Verstovsek,[13] Ron Hoffman,[1] Mohamed E Salama,[13] Dong Chen,[14] Pietro Taverna,[15] Alex Chang,[15] Gozde Colak,[15] Sandra Klein,[15] Vikas Gupta[16]

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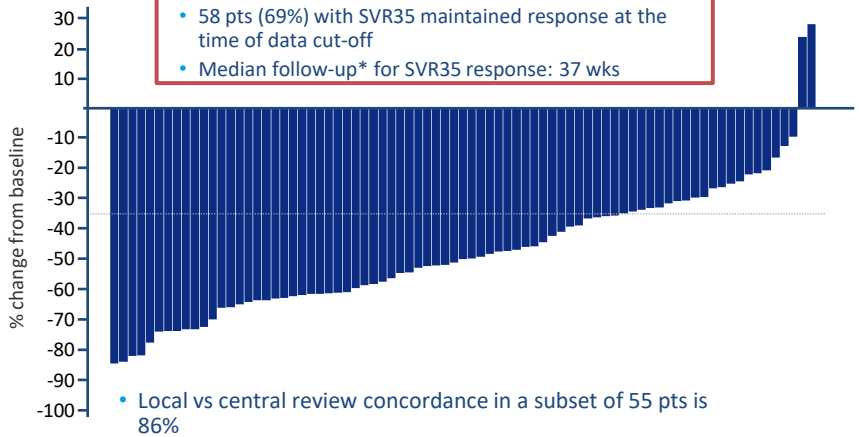
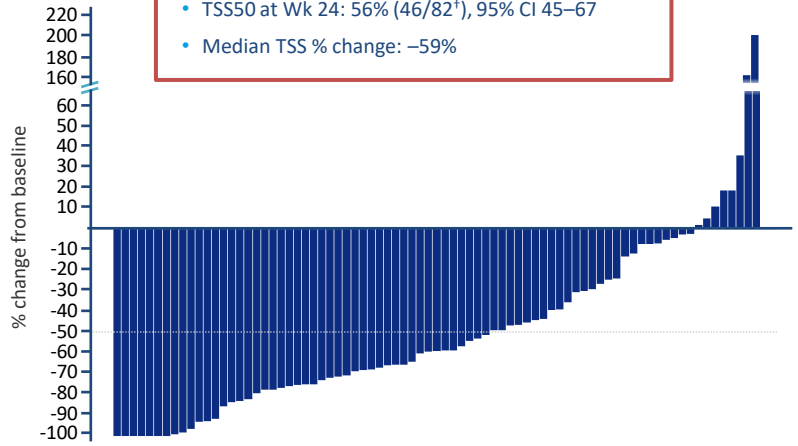
Arm 3: JAKi-naïve MF patients — Reduction of spleen volume and total symptom score in majority of the patients

- SVR35 at Wk 24: 68% (57/84), 95% CI 57–78
- SVR35 at any time: 80% (67/84, range: 10–51 wks)
- Median SVR: –50%
- 58 pts (69%) with SVR35 maintained response at the time of data cut-off
- Median follow-up* for SVR35 response: 37 wks



- Local vs central review concordance in a subset of 55 pts is 86%

- TSS50 at Wk 24: 56% (46/82†), 95% CI 45–67
- Median TSS % change: –59%



SVR per local radiology review; central radiology review is ongoing.
Patients are evaluable for SVR35 or TSS50 at Wk 24 if they have had Wk 24 assessment by the data cut-off date or discontinued without Wk 24 assessment at any time.
*Reverse Kaplan–Meier estimate of median duration of follow-up for SVR35 response.
†Two ongoing patients were nonevaluable for TSS50 at Wk 24; n=1 due to missing baseline, n=1 due to baseline TSS=0.
CI, confidence interval; JAKi, Janus kinase inhibitor; MF, myelofibrosis; pts, patients; SVR, spleen volume reduction; SVR35, ≥35% reduction in spleen volume from baseline; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline; wk, week.

S197

Navitoclax Plus Ruxolitinib in JAK Inhibitor-Naïve Patients With Myelofibrosis: Preliminary Safety and Efficacy in a Multicenter, Open-label Phase 2 Study

Francesco Passamonti[1], James Foran[2], Anand Tandra[3], Valerio De Stefano[4,5], Maria Laura Fox[6], Ahmad Mattour[7], Mary Frances McMullin[8], Andrew C. Perkins[9], Gabriela Rodriguez-Macías[10], Hassan Sibai[11], Qin Qin[12], Avijeet Chopra[12], Jalaja Potluri[12], Jonathan How[13]

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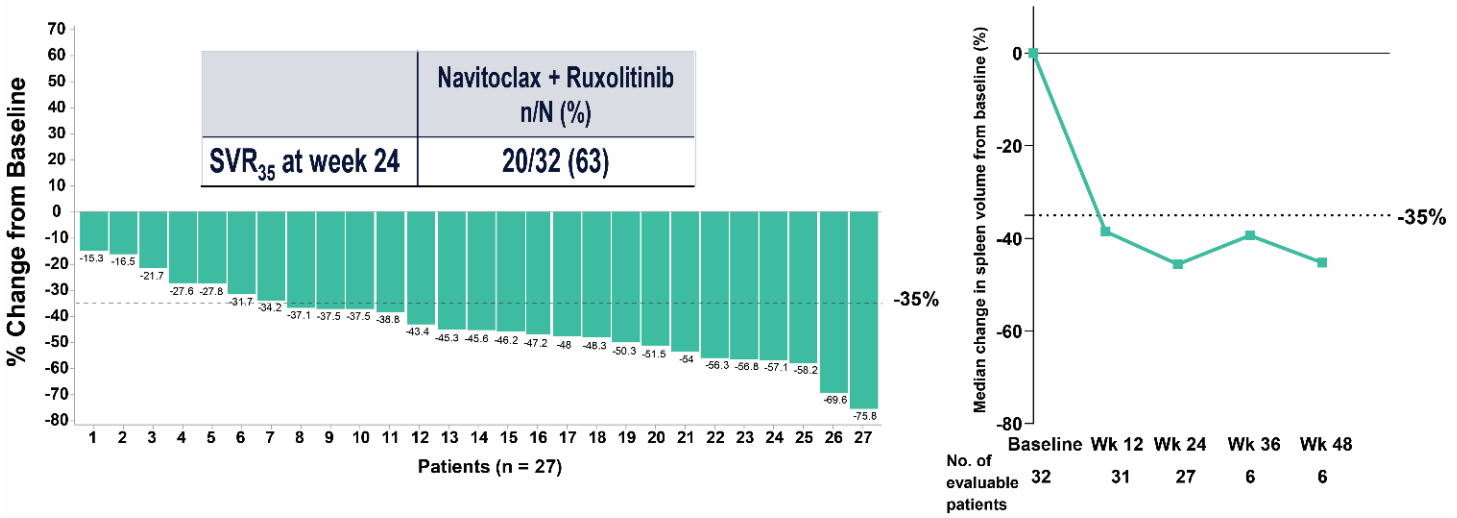
European Hematology Association Congress, June 11, 2022, Vienna, Austria

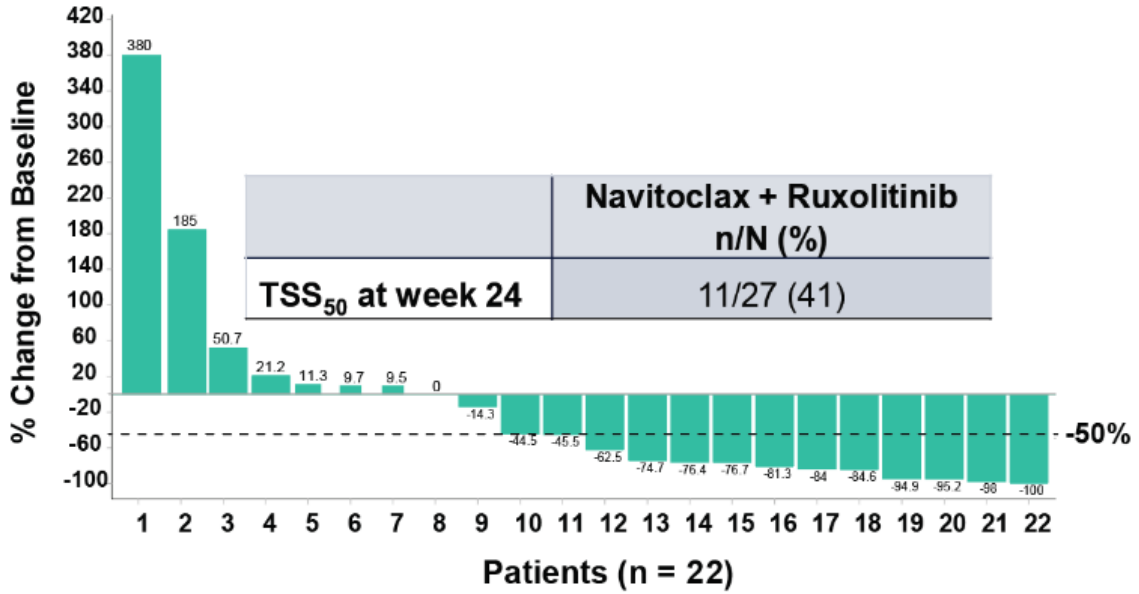
Patients treated with navitoclax and ruxolitinib achieved spleen volume reductions



- All patients experienced reduction in spleen volumes; 20/32 (63%) achieved spleen volume reduction of at least 35% (SVR_{35}) at week 24
- SVR_{35} obtained anytime during the post-baseline period was observed in 25/32 (78%) patients
- Median time to first SVR_{35} was 12.3 weeks (range, 11.1 to 47.3)
- Estimated rate of maintaining SVR_{35} at 12 months was 92.9% (95% CI, 59.1 to 99.0)

Spleen volume was measured by MRI/CT
Three patients discontinued the study prior to week 24, and 2 patients received new anti MF therapy before week 24

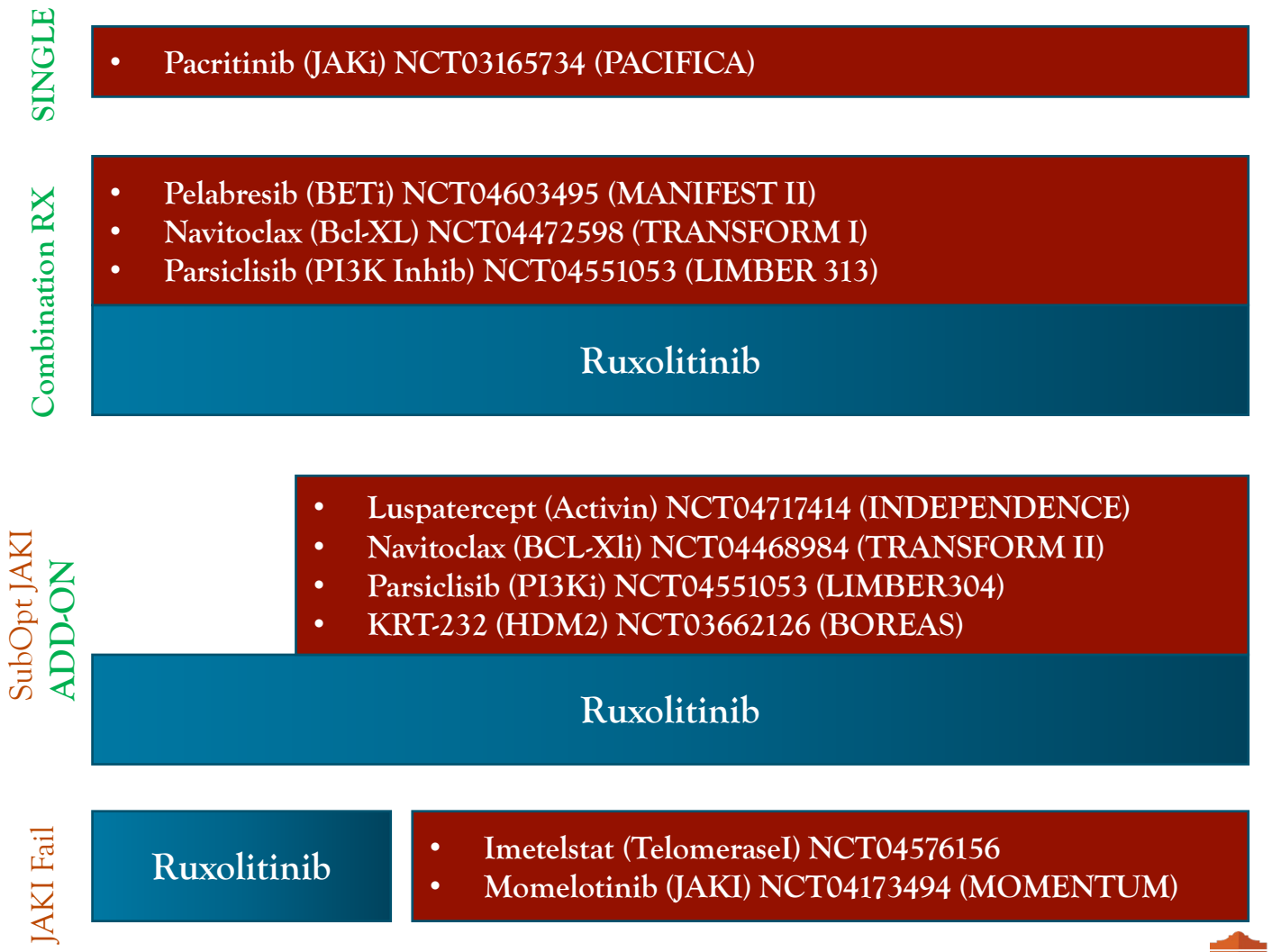
Patients treated with navitoclax and ruxolitinib reported reduction in disease symptom burden



- Total symptom score reduction of at least 50% (TSS_{50}) at anytime during the post-baseline period was observed in 18/27 (67%) patients
- Median time to first TSS_{50} from baseline was 3.2 weeks (95% CI, 0.3 to 16.3)

Total symptom score (TSS) was measured by Myelofibrosis Symptom Assessment Form v.4.0.; 5 patients had baseline TSS ≤ 0 or had missing values for baseline TSS; 5 patients had missing post-baseline TSS at week 24 and were considered as non-responders

Current Phase III trials in MF



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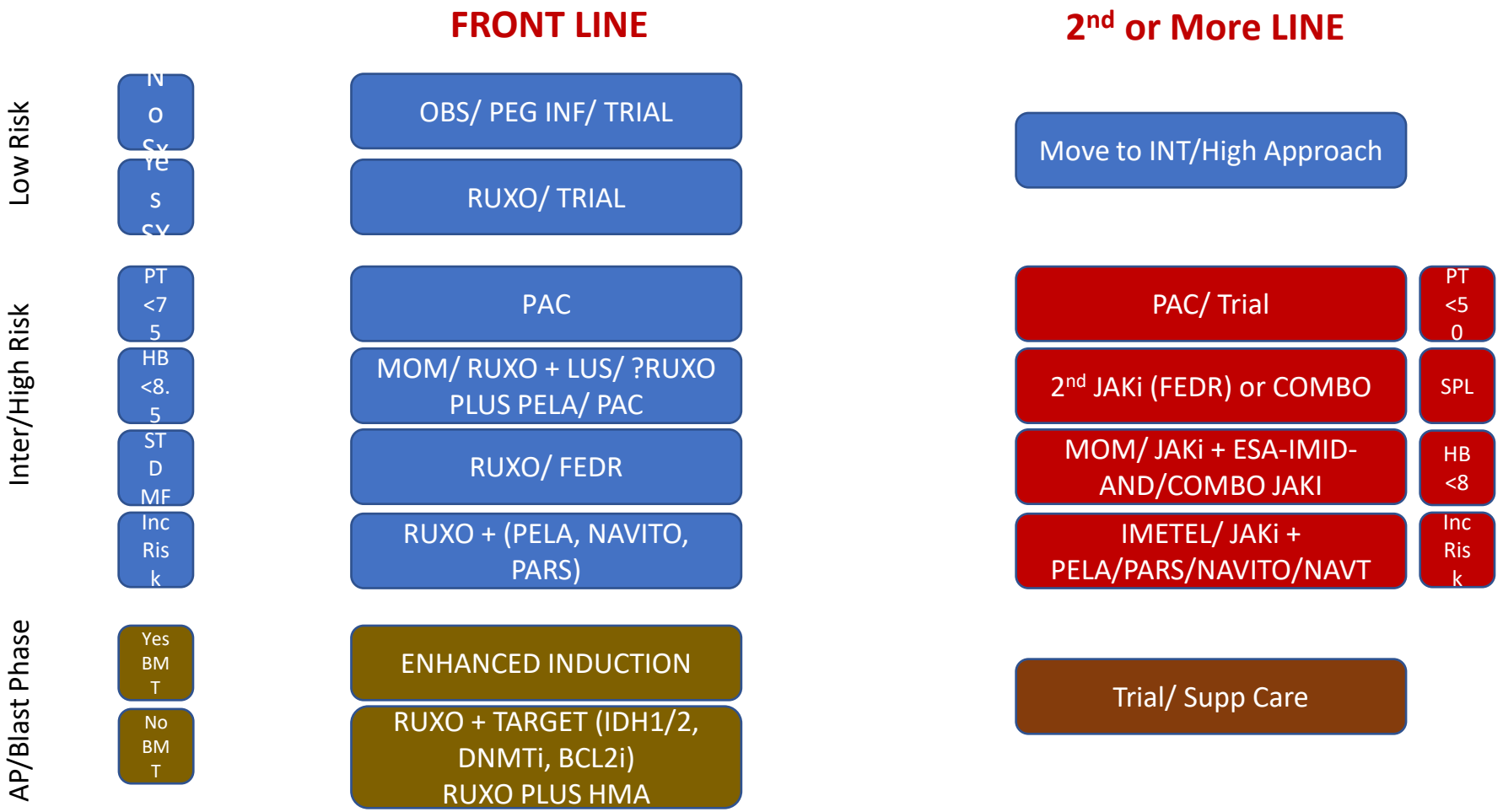
Therapy of MPNs 2022

- Goals and Targets
- ET and PV
- JAK Inhibitors as Foundation
- Non JAKi MOA
- Putting it all Together

MF Treatment in 3-5 Years (Where Transplant Not Selected)



What is Precise and Personalized Cancer Care?

Molecular Features of Disease
-Multi-Omic
-Dx, treatment, survivorship

Communication
Social DOH
Health Literacy

Individual Health Factors In Treatment Planning?

Geography
Employment
Financial Pressures

Individualized Supportive Care Needs?

Individual Cultural Value Factors In Treatment Planning?

Individualized Survivorship?

Disease impact
Symptoms
QoL?

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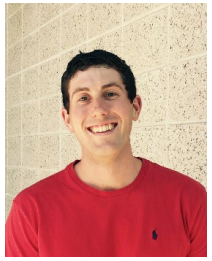
MPN Patient Community

MPN Group	Focus	Website
MPN Research Foundation	RES-ED-ADV	www.Mpnresearchfoundation.org
Leukemia and Lymphoma Society*	RES-ED-ADV	www.lls.org
MPN Advocacy & Education International*	ED-ADV	www.mpnadvocacy.com
MPN Education Foundation*	ED-COMM	www.mpninfo.org
AAMDS Foundation	ED	www.aamds.org
MPN Voice	ED	www.mpnvoice.org.uk
MPN HUB*	ED	www.mpn-hub.com
MPN Advocates Network	ED-ADV	www.mpn-advocates.net
Global MPN Scientific Foundation*	RES-ED-ADV	www.gmpnsf.org
MPN Forum Facebook Group	ED-COMM	https://www.facebook.com/groups/ourmpnforum/

MPN QoL STUDY GROUP



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