MPN Roundtable Year in Review: The Impact of New Data in Myelofibrosis on the Evolving Treatment Landscape

Supplemental Slides

MediCom Worldwide, Inc.

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Program Introduction

- This discussion will review key data and clinical applications of new advances in myelofibrosis, presented at this year's major congresses in hematology
- Topics include:
  - Recent findings in JAK2 inhibitor therapy and the evolving role of these agents in the current treatment paradigm
  - Novel approaches in the treatment of myelofibrosis and their relevance to clinical practice

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Peri-Transplant Administration of Ruxolitinib Is Safe and Feasible in Patients with Myelofibrosis: Primary Results of a Pilot Open-Label Study of Ruxolitinib Administration in Combination with Reduced Intensity Conditioning

ASH 2019 Abstract 669

Haris Ali, MD, David Snyder, MD, Tracy Stiller, MS, Timothy Synold, PhD3, Saloomeh Mokhtari, Joycelynne Palmer, PhD, Amandeep Salhotra, MD, Vinod A. Pullarkat, MD, Ji-lian Cai, MD, Stephen J Forman, MD, Matthew Mei, MD and Ryotaro Nakamura, MD

Ali H, et al. ASH 2019. Abstract 669.

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Peri-Transplant Administration of Ruxolitinib in MF: Study Design

Study objective:

- To identify the maximum tolerated dose and recommended phase 2 dose

Methods:

- Ruxolitinib was given at two dose levels of 5 and 10 mg BID, starting from day -3 pre-HCT until day +30 post-HCT, then tapered off by day +33
- Dose levels were chosen based on previous retrospective studies identifying the drug dose for treatment of GVHD

Primary endpoint:

- Safety

Key secondary endpoints:

- Grade 2-4 acute GVHD, engraftment, infection, OS, PFS, non-relapse mortality, relapse and chronic GVHD

Ali H, et al. ASH 2019. Abstract 669.

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Efficacy Results

- Twelve patients have been enrolled, six in each treatment arm
- Median age at the time of HCT: 53 years (range: 25-66) for the 5 mg group: 68 years (range: 56-72) for the 10 mg group

Measure, %	Patients (N=12)
One-year OS	80
PFS	68
Non-relapse mortality	21

- All 12 patients engrafted
  - Median time to neutrophils engraftment: 19 days (range: 13-23) for the 5 mg arm; 16 days (range: 12-22) for the 10 mg arm

Ali H, et al. ASH 2019. Abstract 669.

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Safety Results

- Hematologic DLTs were not observed in patients at either dose level

Measure	Ruxolitinib 5 mg (n = 6)	Ruxolitinib 10 mg (n=6)
Grade ≥3 toxicities, n	• Cardiac (1) • Pulmonary (1) • GI (1)	• Pulmonary (1)
Deaths, n	• Respiratory failure (1)	• Acute GHVD (1)
Median time to GHVD onset, days	20	51

- Grade 3-4 acute GVHD was seen in only one out of 12 patients; grade 1 acute GVHD was seen in four patients
- CMV infection was seen in only one patient at DL2

Ali H, et al. ASH 2019. Abstract 669.

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PK Findings

- PK studies were performed for five patients in the 5 mg arm and all patients in the 10 mg dose
- PK was dose-proportional
- The half-lives and oral clearances were similar between the two dose groups
- The Cmax and AUC were lower vs previously published results in healthy volunteers
- The elimination half-life was similar to published data
  - The lower drug exposures measured on the current trial is most likely due to decreased oral absorption
- GVHD biomarkers and inflammatory cytokines levels were similar between the dose groups

Ali H, et al. ASH 2019. Abstract 669.

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Safety and Efficacy of Ruxolitinib (Rux) in Patients with Myelofibrosis (MF) and Anemia (Hb <10 g/dL): Results at Week (WK) 24 of the REALISE Trial

EHA 2019 Abstract PS1465

Francisco Cervantes, Heinz Gisslinger, Atanas Radinoff, Francesco Passamonti, Lynda Foltz, David M. Ross, Nicola Vianelli, Francesco Mannelli, Pierre Zachee, Alexandr Myasnikov, Evren Zor, Geralyn Gilotti, Ranjan Tiwari, Haifa Kathrin Al-Ali

Cervantes F, et al. EHA 2019. Abstract PS1465.

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Alternative Ruxolitinib Dosing Regimen in Patients with MF and Anemia: Study Design

Study objective:

- To evaluate the safety and efficacy of an alternative ruxolitinib dosing regimen in patients with myelofibrosis and anemia

Inclusion criteria:

- Patients with PMF, post-ET MF or post-PV MF, palpable (≥5 cm) spleen, Hb level <10 g/dL and platelet count ≥50 x 10^9/L

Methods:

- Patients were started on ruxolitinib 10 mg BID
- After 12 weeks, up titrations to 15 or 20 mg BID were allowed based on efficacy and platelet counts

Primary endpoint:

- The proportion of patients achieving ≥50% reduction in spleen length (SL) at week 24

Cervantes F, et al. EHA 2019. Abstract PS1465.

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REALISE Trial: Efficacy Results

- 51 patients were included; median duration of exposure to RUX: 38.0 weeks
- At week 24, 28 patients had ≥50% SL reduction
  - Five patients had reductions of 25 to 50%
- Hb levels dropped in the first eight weeks of treatment, then stabilized; platelet levels remained constant
- At data cutoff, 32 patients were still undergoing treatment; 19 had discontinued
- 6/8 transfusion-dependent patients at baseline had a ≥50% SL reduction at week 24
- 17/24 non-transfusion-dependent patients at baseline had a ≥50% SL reduction at week 24
- 11 NTD patients at baseline became TD

Cervantes F, et al. EHA 2019. Abstract PS1465.

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REALISE Trial: Safety Findings

- 23 patients had ≥1 dose reduction or interruption most commonly due to AEs (n=13; 10 were hematological)
- Most common grade 3/4 hematological AEs:
  - Anemia (27.5%)
  - Thrombocytopenia (13.7%)
- Most common (>10%) non-hematological AE: fatigue (11.8%)
- Improvements in symptoms were also seen at week 24 in patient-reported outcomes

Cervantes F, et al. EHA 2019. Abstract PS1465.

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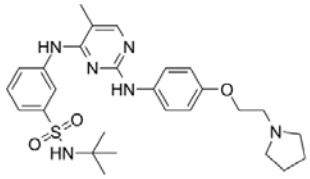
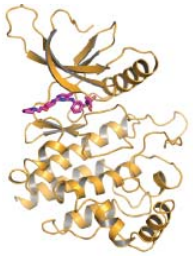
Fedratinib

- 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[1]
- Higher inhibitory activity for *JAK2* over *JAK1, JAK3*, and *TYK2*[2]
- Fedratinib was investigated for treatment of MF in JAK-inhibitor-naïve patients in the phase 3 JAKARTA trial,[3] and in patients previously treated with RUX in the phase 2 JAKARTA2 trial[4]
- JAKARTA and JAKARTA2 allowed enrollment of patients with platelet counts of ≥50 × 10^9/L at study entry[3,4]

OBJECTIVE: Assess the efficacy and safety of fedratinib 400 mg/day in JAKARTA or JAKARTA2 patients with BL platelet counts of 50 to <100 × 10^9/L or ≥100 × 10^9/L



FEDRATINIB



JAK2 KINASE DOMAIN – Fedratinib Complex[5]

[1] INREBIC® (fedratinib) prescribing information. Celgene Corporation; 08/2019. [2] Wernig G, et al. *Cancer Cell*. 2008;13:311-320. [3] Pardanani A, et al. *JAMA Oncol*. 2015;1:643-651. [4] Harrison C, et al. *Lancet Haematol*. 2017;4:e317-324. [5] Hantschel O. *ACS Chem Biol*. 2015;10:234-245.

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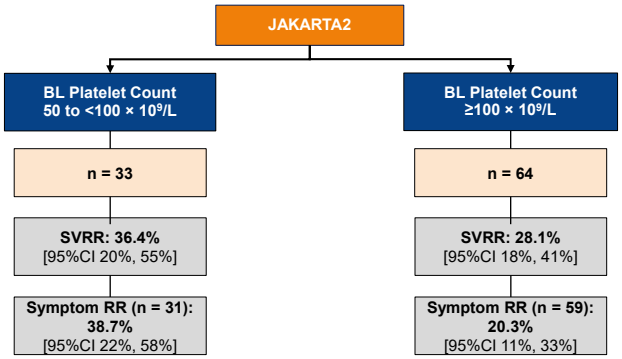
JAKARTA2: Efficacy Results

- SVRR was 31% (95% CI 22%, 41%) and symptom RR was 27% (18%, 37%)
- There was no statistically significant difference in SVRR or symptom RR between BL platelet count subgroups



Statistical comparisons between BL platelet count subgroups should be interpreted with caution due to small sample sizes.
Harrison CN, et al. *Lancet Haematol*. 2017;e317-e324.

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JAKARTA2 Re-analysis

- Definitions of prior ruxolitinib treatment outcomes according to original study criteria (ITT population) and new stringent definitions of ruxolitinib relapsed, refractory, or intolerant (stringent criteria cohort)

ITT Population (N = 97)	Stringent Criteria Cohort (n = 79)
Ruxolitinib resistant or intolerant to ruxolitinib per investigator assessment: –**Resistant**: No response, stable disease, evidence of disease progression, or loss of response following ruxolitinib exposure for ≥14 days –**Intolerant**: Discontinuation due to unacceptable toxicity after any duration of RUX treatment	**Relapsed**: RUX treatment for ≥3 months with regrowth (<10% SVR or <30% spleen size decrease rom BL), following an initial response. Response to RUX is defined as ≥50% reduction in spleen size for BL spleens >10 cm (or ≥35% reduction from BL spleen volume); a non-palpable spleen for BL spleen size between 5–10 cm; or not eligible for spleen response for BL spleen <5 cm
	Refractory: Ruxolitinib treatment for ≥3 months with <10% SVR or <30% decrease in spleen size from BL
	Intolerant: Ruxolitinib treatment for ≥28 days complicated by development of RBC transfusion requirement (≥2 units per month for ≥2 months); or grade ≥3 thrombocytopenia, anemia, hematoma and/or hemorrhage while receiving ruxolitinib

Harrison CN, et al. EHA 2019. Abstract 1459.

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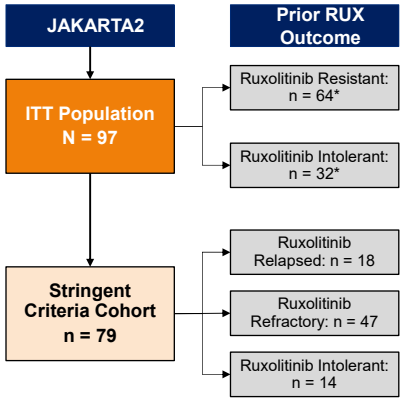
JAKARTA2 Re-analysis: Results



		Stringent Criteria Cohort (n = 79)	
Resistant, n (%)	**64 (66)**	**Refractory, n (%)**	**47 (60)**
Lack of response	24 (25)		
Disease progression	15 (16)	**Relapsed, n (%)**	**18 (23)**
Loss of response	25 (26)		
Intolerant, n (%)	**32 (33)**	**Intolerant, n (%)**	**14 (18)**
Hematologic toxicity	25 (26)	Development of RBC transfusion need	6 (8)
Thrombocytopenia	13 (13)		
Anemia	9 (9)	Toxicity	8 (10)
Other	3 (3)	Thrombocytopenia	3 (4)
Other toxicity	7(7)	Anemia	5 (6)
Other, n (%)	**1 (1)**		
Lack of efficacy	1 (1)		

*One patient categorized as "Other: lack of efficacy"
Harrison CN, et al. EHA 2019. Abstract 1459.

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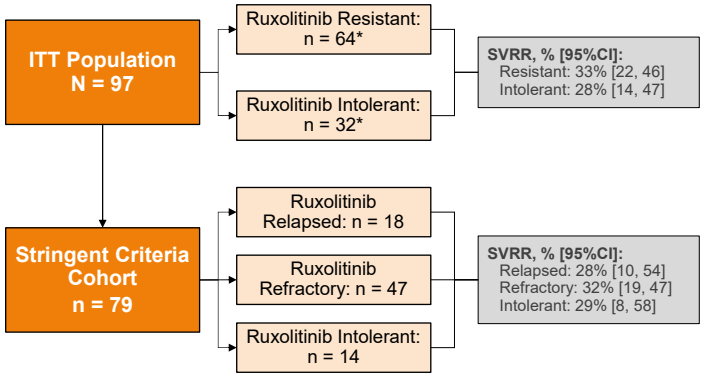
Spleen Volume Response Rates by Prior Ruxolitinib Outcomes: ITT Population and Stringent Criteria Cohort



*One patient categorized as "Other: lack of efficacy"
Harrison CN, et al. EHA 2019. Abstract 1459.

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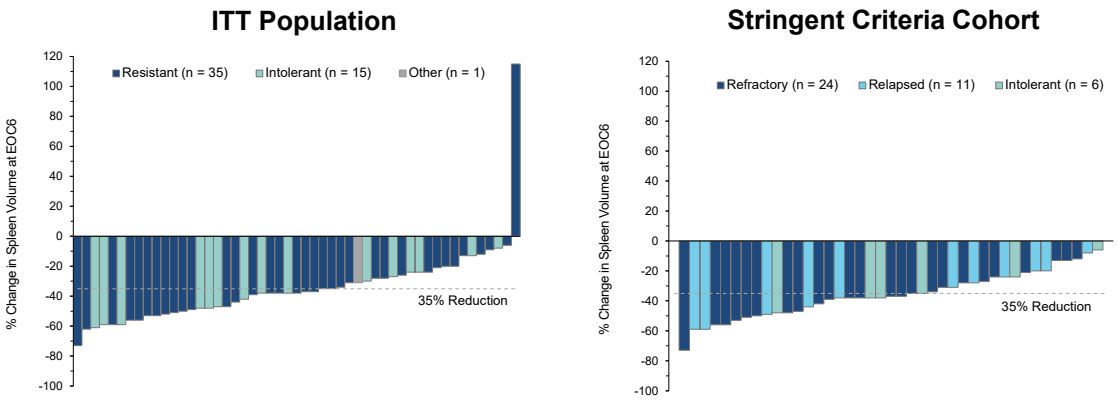
Individual Changes in Spleen Volume from Baseline to End of Cycle 6*



*Among patients with spleen volume assessments at both time points (baseline and end of cycle 6)
Harrison CN, et al. ASH 2019. Abstract 4165.

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Thrombocytopenia

- JAKARTA[1]:
  - Grade 3-4 thrombocytopenia events in the fedratinib 400 mg/day arm led to dose modification in one patient and permanent treatment discontinuation in two patients; these three patients had BL platelet counts <100 × 10^9/L
- JAKARTA2[2]:
  - Grade 3-4 thrombocytopenia events led to dose modification in four patients (three had BL platelet counts of 50 to <100 × 10^9/L) and treatment discontinuation in two patients (one had BL platelet count <100 × 10^9/L)

Grade 3–4 Thrombocytopenia in Patients with BL Platelet Counts of 50 to <100 × 10^9/L

	JAKARTA		JAKARTA2
	Placebo n = 18	Fedratinib 400 mg n = 14	Fedratinib 400 mg n = 33
Thrombocytopenia	4 (22)	4 (29)	16 (49)

[1] Pardanani A, et al. *JAMA Oncol.* 2015;1:643-651. [2] Harrison CN, et al. *Lancet Haematol.* 2017;4:e317-e324.

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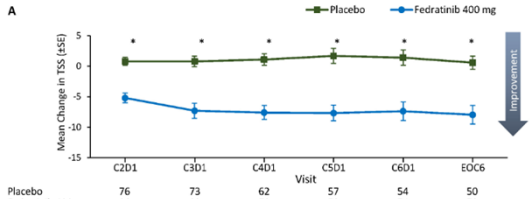
HRQoL Findings from the JAKARTA Trials

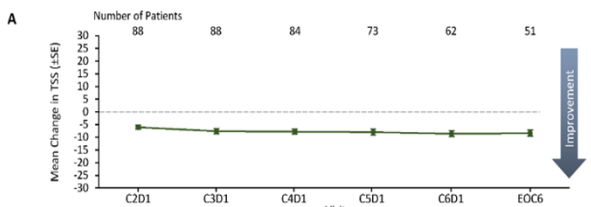
- In both JAKARTA studies, the effect of fedratinib on patient-reported MF symptoms and HRQoL were assessed with the modified MFSAF

Figure. A) Mean change from baseline in modified MFSAF total symptom score by visit; and B) Forest plot of symptom improvement at the end of cycle 6 in select clinically meaningful patient subgroups



	C2D1	C3D1	C4D1	C5D1	C6D1	EOC 6
Effect Size	-0.46	-0.63	-0.68	-0.73	-0.69	-0.67
95% CI	-0.76, -0.17	-0.94, -0.33	-0.98, -0.38	-1.03, -0.43	-0.99, -0.38	-0.97, -0.36

Figure. A) Mean change from baseline in modified MFSAF total symptom score by visit; and B) Forest plot subgroup analyses of symptom improvement (≥50% reduction from baseline MFSAF total symptom score) at the end of cycle 6



	C2D1	C3D1	C4D1	C5D1	C6D1	EOC 6
Effect Size	-0.50	-0.62	-0.64	-0.66	-0.70	-0.68
95% CI	-0.72, -0.28	-0.84 -0.39	-0.87, -0.40	-0.91, -0.41	-0.98, -0.43	-0.98, -0.38

[1] Mesa R, et al. ASH 2019. Abstract 704. [2] Harrison CN, et al. ASH 2019. Abstract 2207.

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Summary of the JAKARTA Trials

- Treatment with fedratinib in JAKARTA2 patients who were previously treated with ruxolitinib was associated with a robust spleen response rate, similar to or higher than rates seen with other JAK inhibitors when used as frontline therapy for MF6–8
- During fedratinib treatment, about one-third of patients in JAKARTA2 achieved a spleen volume response and most experienced some degree of spleen volume reduction, regardless of whether they were relapsed, refractory, or intolerant to prior ruxolitinib therapy
- Treatment-emergent adverse event frequencies were generally similar among patients who were relapsed, refractory, or intolerant to prior ruxolitinib treatment
- Outcomes of long-term fedratinib treatment in patients previously treated with ruxolitinib are currently under study in the phase 3 FREEDOM and FREEDOM2 trials (NCT03755518, NCT03952039)

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What Is the Role of Fedratinib in the Current Treatment Paradigm for MF?

- Current evidence indicate that fedratinib is an important second-line consideration and that it is a guideline-supported frontline option for patients
- Data from the JAKARTA trials suggest that the agent may be used in full dose in patients with a platelet count between 50 and 100,000

- Recommendations in the management of patients on fedratinib therapy:
  - Check thiamine levels before stating therapy and advise patients to take thiamine supplements while on therapy
  - Prescribe antiemetic or anti-diarrheal medications when needed to treat GI side effects

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Pacritinib Demonstrates Efficacy Versus Best Available Therapy in Myelofibrosis Patients with Severe Thrombocytopenia in Two Phase 3 Studies

ASH 2019 Abstract 4195

Ruben A. Mesa, MD, Moshe Talpaz, MD, Jean-Jacques Kiladjian, MD, PhD, Claire N Harrison, Professor, Srdan Verstovsek, MD, PhD, Sarah A Buckley, MD, Karisse Roman-Torres and John Mascarenhas, MD

Mesa RA, et al. ASH 2019. Abstract 4195.

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Pacritinib: The PERSIST Trials

- Pacritinib: oral *JAK2/IRAK1* inhibitor that was evaluated for SVR and TSS in two phase 3 studies in patients with MF, patients, including those with severe thrombocytopenia
- PERSIST-1 included JAK inhibitor-naive patients with no lower platelet limitation
- PERSIST-2 was limited to patients with a platelet count <100,000/μL, with or without prior JAK inhibitors (eg, ruxolitinib)
- To better evaluate PAC in MF patients with baseline platelet count <50,000/μL, a retrospective pooled analysis was performed on data from both PERSIST trials
- Clinical trial outcomes from this high-risk MF population have not previously been reported

Mesa RA, et al. ASH 2019. Abstract 4195.

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The PERSIST Trials: Efficacy Findings

	Pooled Pacritinib 400 mg QD and 200 mg BID	Pooled Pacritinib 400 mg QD	Pacritinib 200 mg BID	Pooled BAT *
SVR				
N, ITT efficacy population	104	73	31	48
N (%) with ≥35% SVR	24 (23%)	15 (21%)	9 (29%)	1 (2%)
Difference pacritinib-BAT, % CI	21.0 (9.8, 29.3)	18.5 (5.0, 29.6)	25.9 (4.3, 44.5)	--
P value vs BAT	0.0007	0.0025	0.0059†	--
TSS				
N, ITT efficacy population	80	49	31	37
N (%) with improvement in TSS	16 (20%)	9 (18%)	7 (23%)	4 (11%)
Difference pacritinib-BAT, % CI	9.2 (-5.8, 21.6)	7.6 (-10.5, 24.1)	10.1 (-12.0, 31.1)	--
P value vs BAT	0.2944	0.3793	0.372‡	--

*Includes ruxolitinib
†*P* values is compared to BAT from the PERSIST-1 study. 1/32 (3%) BAT patients with platelets <50,000/μL had a ≥35% SVR in PERSIST-2
‡*P* values is compared to BAT from the PERSIST-2 study. 4/32 (13%) BAT patients <50,000/μL had a ≥50% improvement in TSS PERSIST-2
Mesa RA, et al. ASH 2019. Abstract 4195.

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PERSIST Trials: Safety Data

The safety profile in patients with severe thrombocytopenia was generally manageable and consistent with the overall study population from the PERSIST trials

GI events were the most common TEAE but were primarily grade 1/2 and rarely required dose reduction or discontinuation

Grade 3/4 hemorrhages: 14% of patients on PAC vs 14% on BAT

Grade 3/4 cardiac events: 8% of PAC patients vs 12% on BAT

Deaths on study or within 30 days of last study dose occurred in 23 (17%) PAC patients vs 8 (14%) BAT

- Of these deaths, three (2%) PAC patients and two (4%) BAT patients had grade 5 hemorrhagic events
- Grade 5 cardiac events occurred in four (3%) PAC patients and four (7%) BAT patients

Mesa RA, et al. ASH 2019. Abstract 4195.

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Results of PAC203: A Randomized Phase 2 Dose-Finding Study and Determination of the Recommended Dose of Pacritinib

ASH 2019 Abstract 667

Aaron T. Gerds, MD, MS, Michael R. Savona, MD, Bart L. Scott, MD, Moshe Talpaz, MD , Miklos Egyed, Claire N Harrison, Professor, Abdulraheem Yacoub, MD, Alessandro M. Vannucchi, MD, Adam J. Mead, MBBChir, Jennifer O'Sullivan, Sarah A Buckley, MD, Diane R. Mould, PhD, Shanthakumar Tyavanagimatt, PhD, Jennifer A. Smith, PhD and John Mascarenhas, MD

Gerds AT, et al. ASH 2019. Abstract 667.

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PAC203: Pacritinib Dose-Finding Trial

Study population:

- Patients with DIPSS intermediate-1, -2, or high-risk MF who were intolerant of or failed to benefit from ruxolitinib

Study design:

- Patients were randomized 1:1:1 to PAC 200 mg BID, 100 mg BID, or 100 mg QD stratified by baseline platelet count

Efficacy endpoints:

- Proportion of patients with ≥35% SVR
- Proportion with ≥50% TSS reduction

Gerds AT, et al. ASH 2019. Abstract 667.

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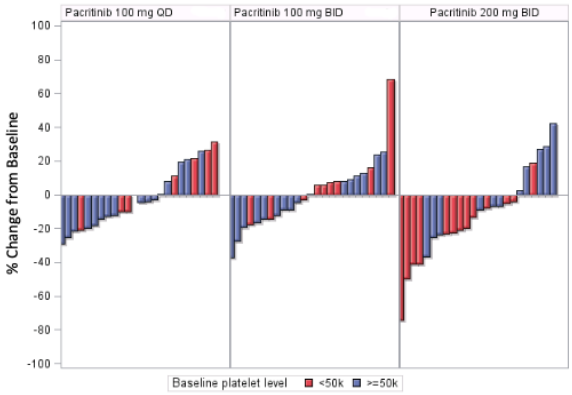
PAC203: Efficacy Results

- 164 patients were included; 161 received treatment

Figure 1. Percent Change in Spleen Volume Between Baseline and 24 Weeks by Treatment Arm



Gerds AT, et al. ASH 2019. Abstract 667.

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PAC203: Safety Results

- The most common non-hematologic TEAEs were GI and were distributed similarly across arms
- The most common hematologic AEs were thrombocytopenia and anemia, both occurring at higher frequencies at 200 mg BID
  - This did not lead to higher rates of grade 3/4 hemorrhage at higher doses
  - The highest dose saw no excess in grade 3/4 cardiac or infectious AEs
- In this cohort of advanced MF patients, there were seven grade 5 (fatal) AEs:
  - Two at 200 mg BID (sepsis, subdural hematoma)
  - Three at 100 mg BID (disease progression, subdural hematoma, heart failure)
  - Two at 100 mg QD (sepsis, tuberculosis)

Gerds AT, et al. ASH 2019. Abstract 667.

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What Is the Clinical Relevance of These Data?

- Pacritinib 200 mg BID is generally well tolerated and demonstrated clinical activity, particularly in patients with severe thrombocytopenia (platelet count <50,000/mL)
- In this population of patients with high-risk, advanced, and heavily pre-treated disease, PAC 200 mg BID was associated with reduction in spleen size and symptom burden

Gerds AT, et al. ASH 2019. Abstract 667.

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Dynamic and Time-to-Event Analyses Demonstrate Marked Reduction in Transfusion Requirements for Janus Kinase Inhibitor–Naïve Myelofibrosis Patients Treated with Momelotinib Compared Head to Head with Ruxolitinib

ASH 2019 Abstract 1663

Ruben A Mesa, MD, John Catalano, MBBS, FRACP, FRCPA, Francisco Cervantes, MD, Timothy Devos, MD, PhD, Jason Gotlib, MD, MS, Jean-Jacques Kiladjian, MD, PhD, Donal P. McLornan, MB, BCh (Hons), MRCP, PhD, FRCPath, Kazuya Shimoda, MD, PhD, Elisabeth Coart, PhD, Koenraad D'Hollander, MD, MSC, Rafe Donahue, PhD and Mark M Kowalski, MD, PhD

Mesa RA, et al. ASH 2019. Abstract 1663.

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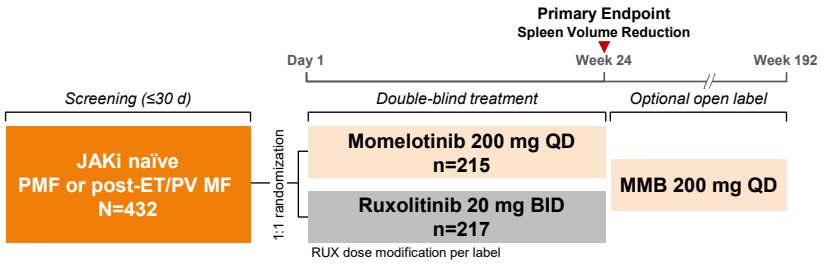
SIMPLIFY-1 Study Design



- Phase 3, randomized, double blind, active-controlled, multicenter study
- Stratification by:
  - RBC transfusion dependence (yes vs no)
  - Platelets <100 x 10^9/L, ≥100 – ≤200 x 10^9/L, or >200 x 10^9/L
- After completing the 24-week double-blind treatment phase, patients had option to receive open-label MMB for up to an additional 168 weeks

Mesa RA, et al. ASH 2019. Abstract 1663.

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Standard Analyses of the SIMPLIFY-1 Data Demonstrate Momelotinib's Anemia Benefits vs Ruxolitinib

- Relevant baseline characteristics were well balanced, including median hemoglobin levels (10.5 g/dL and 10.3 g/dL) and percentages of TD and TI patients (25% and 24%; and 68% and 70%) for the momelotinib and ruxolitinib groups, respectively
- A variety of standard landmark analyses of anemia benefit were conducted in SIMPLIFY-1, demonstrating consistently positive benefits in favor of momelotinib:

Measure	Momelotinib	Ruxolitinib	*P* Value
% TI at week 24	67	49	<0.001
% TD at weeks 24	30	40	0.019
% TD → TI (rolling 12-week)	49	29	0.0455

Mesa RA, et al. ASH 2019. Abstract 1663.

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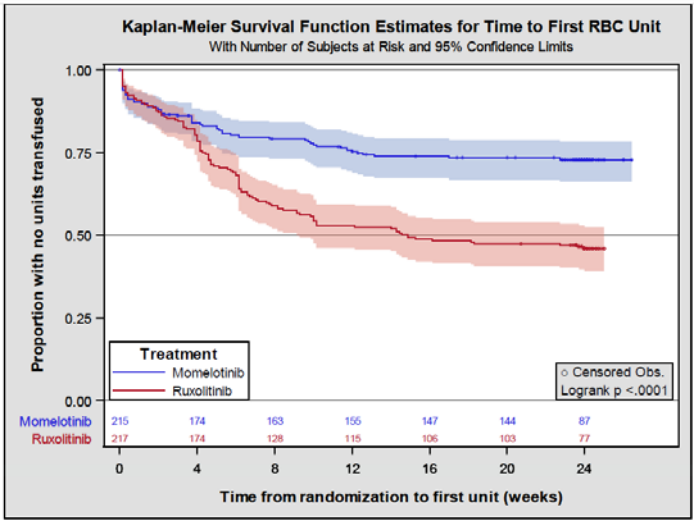
More Patients Require No Transfusions on MMB



Mesa RA, et al. ASH 2019. Abstract 1663.

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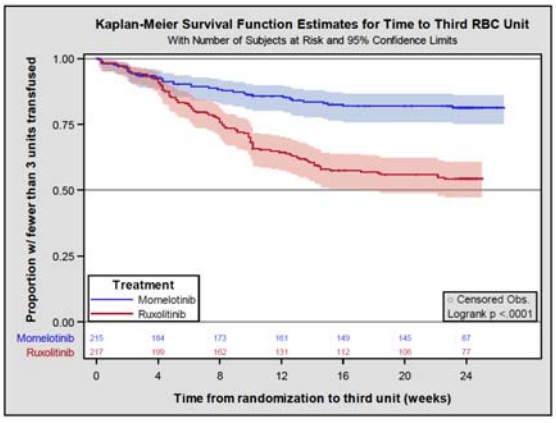
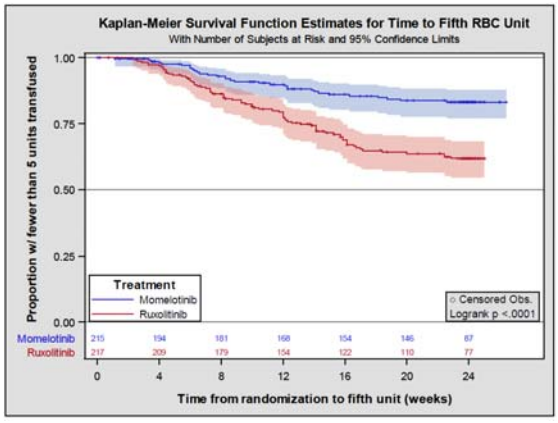
Immediate and Sustained Reduction in Transfusion Burden on MMB

- Odds of receiving <3 transfusions was 3.67 times higher on momelotinib vs ruxolitinib (*P*<.0001)
- Odds of receiving <5 transfusions was 2.99 times higher on momelotinib vs ruxolitinib (62%, *P*<.0001)





Mesa RA, et al. ASH 2019. Abstract 1663.

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What Is the Clinical Relevance of These Data?

- Momelotinib may become a preferred treatment option for MF patients, demonstrating significant anemia benefits including substantively reduced transfusion burden compared directly with ruxolitinib[1]
- Meaningful anemia benefits were achieved while also maintaining clinically comparable benefits on splenomegaly and constitutional symptoms as directly compared to ruxolitinib[1]
- The ongoing phase 3 MOMENTUM trial is evaluating momelotinib vs danazol in patients with symptomatic patients with myelofibrosis and anemia: NCT04173494[2]

[1] Mesa RA, et al. ASH 2019. Abstract 1663. [2] ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04173494.

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Safety and Efficacy of Combined Ruxolitinib and Thalidomide in Patients with Myelofibrosis: A Phase II Study

ASH 2019 Abstract 4163

Raajit K. Rampal, MD, PhD, Srdan Verstovsek, MD, PhD, Sean M. Devlin, PhD, Amber C. King, PharmD, BCOP, Eytan M. Stein, MD, Naveen Pemmaraju, MD, Michael J. Mauro, MD, Tapan M. Kadia, MD8, Guillermo Montalban-Bravo, MD, Kelsey Alvarez, RN, Nicole Ard, Tawni Goodman, Bria Taylor and Prithviraj Bose, MD

Rampal R, et al. ASH 2019. Abstract 4163.

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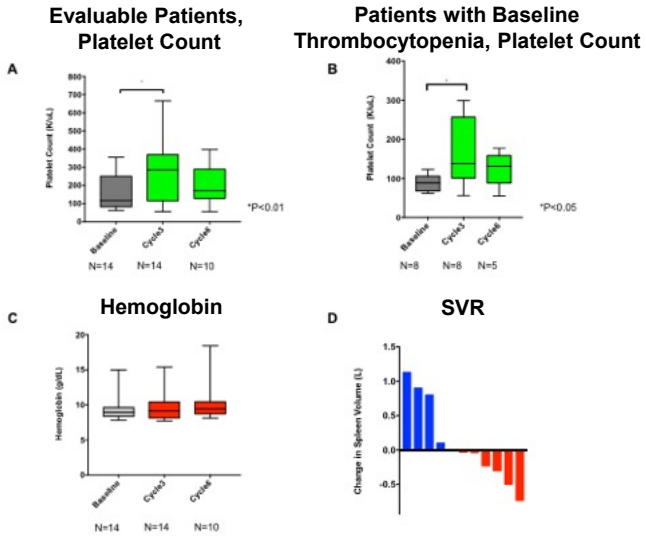
Combined Ruxolitinib and Thalidomide: Results



Rampal R, et al. ASH 2019. Abstract 4163.

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Updated Results from the German Mpnsg-0212 Combination Trial: Ruxolitinib Plus Pomalidomide in Myelofibrosis with Anemia

ASH 2019 Abstract 672

Frank Stegelmann, MD, Steffen Koschmieder, Susanne Isfort, Andreas Hochhaus, MD, Florian H. Heidel, Holger Hebart6, Markus Bangerter, Denise Wolleschak, Christoph Scheid, MD, Joachim R Göthert, PD, MD, Philippe Schafhausen, Thomas Kindler, MD, Markus P. Radsak, MD, Robert Möhle, MD, Cornelius Waller, Nikolas von Bubnoff, Andreas Reiter, Hartmut Döhner, MD, Martin Griesshammer, MD and Konstanze Döhner

Stegelmann F, et al. ASH 2019. Abstract 672.

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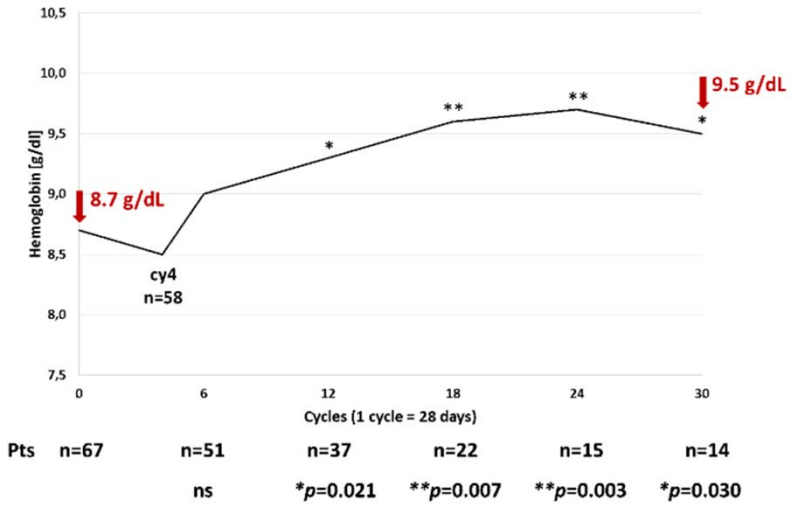
Ruxolitinib Plus Pomalidomide: Results



Stegelmann F, et al. ASH 2019. Abstract 672.

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MANIFEST, a Phase 2 Study of CPI-0610, a Bromodomain and Extraterminal Domain Inhibitor (BETi), as Monotherapy or "Add-On" to Ruxolitinib, in Patients with Refractory or Intolerant Advanced Myelofibrosis

ASH 2019 Abstract 670

John Mascarenhas, Marina Kremyanskaya, Ronald Hoffman, Prithviraj Bose, Moshe Talpaz, Claire Harrison, Vikas Gupta, Brian Leber, Shireen Sirhan, Sujan Kabir, Adrian Senderowicz, James Shao, Jennifer Mertz, Patrick Trojer, Srdan Verstovsek

Mascarenhas J, et al. ASH 2019. Abstract 670.

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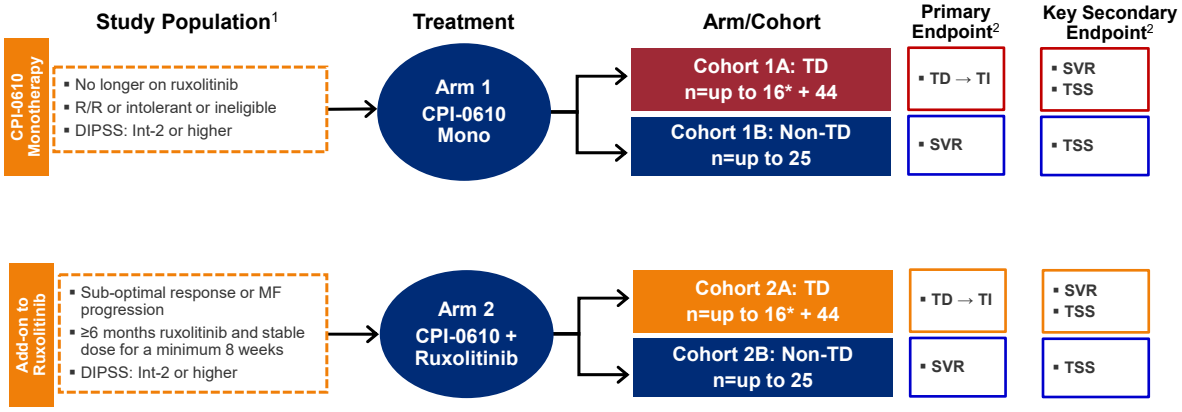
MANIFEST: Study Schema



[1] ClinicalTrials.gov Identifier: NCT02158858 for further details on study design and patient population per last protocol amendment.
[2] Other endpoints: Anemic response, RBC transfusion rate, safety, PK, proinflammatory cytokine levels, bone marrow morphology and mutant allele burden
* Will follow Simon 2-stage design

Mascarenhas J, et al. ASH 2019. Abstract 670.

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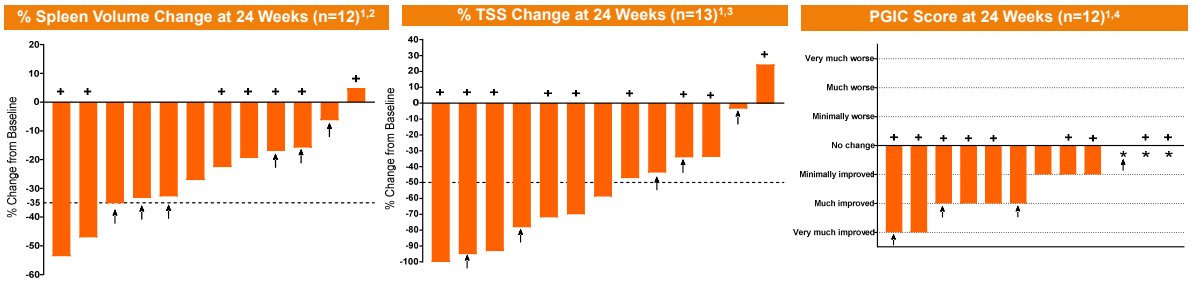
Cohort 2A: CPI-0610 Add-on to Ruxolitinib in R/R MF TD Patients–Efficacy Results at 24 Weeks



- SVR35 Response: 25% (3/12)
- Median Change: -24.9%

- TSS ≥50% Response: 54% (7/13)
- Median Change: -58.8%

- PGIC: 75% (9/12) had improvement in overall status
  - 50% (6/12) much or very much improved

Patients[1] with TD to TI conversion: 6 of 14

[1] Evaluable patients: Patients received at least 24 weeks of treatment, have baseline and post-baseline assessment at 24 weeks available. SVR and TSS: % Change at 24 weeks. PGIC status at 24 weeks. [2] Two patients not included due to missing 24 weeks spleen volume assessment. [3] One patient not included due to missing baseline TSS converted from TD to TI. [4] Two patients not included due to missing 24 weeks PGIC assessment converted from TD to TI.
Preliminary data as of 17 October 2019

Mascarenhas J, et al. ASH 2019. Abstract 670.

+ HMR
↑ TD→TI Conversion
* Patients with no change

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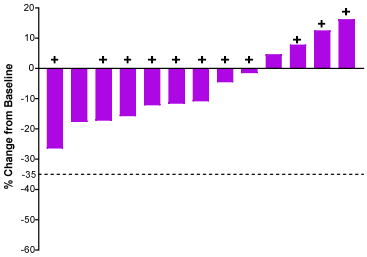
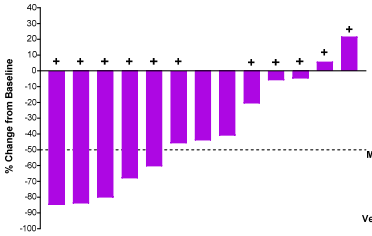
Cohort 2B: CPI-0610 Add-on to Ruxolitinib in R/R MF Non-TD Patients–Efficacy Results at 24 Weeks

% Spleen Volume Change at 24 Weeks (n=13)[1]



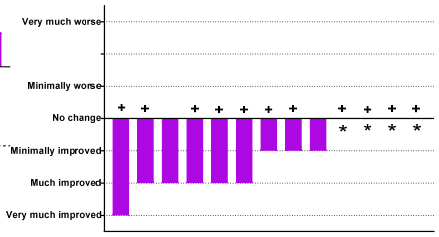
- SVR35 Response: 0/13
- Median Change: -10.9%

% TSS Change at 24 Weeks (n=13)[1]



- TSS ≥50% Response: 38% (5/13)
- Median Change: -44.1%

PGIC Score at 24 Weeks (n=13)[1]



- PGIC: 69% (9/13) had improvement in overall status
  - 46% (6/13) much or very much improved

[1] Evaluable patients: Patients received at least 24 week of treatment, have baseline and 24 weeks post baseline assessment available
SVR and TSS: % Change at 24 weeks. PGIC status at 24 weeks.
Preliminary data as of 17 October 2019

Mascarenhas J, et al. ASH 2019. Abstract 670.

+ HMR

* Patients with no change

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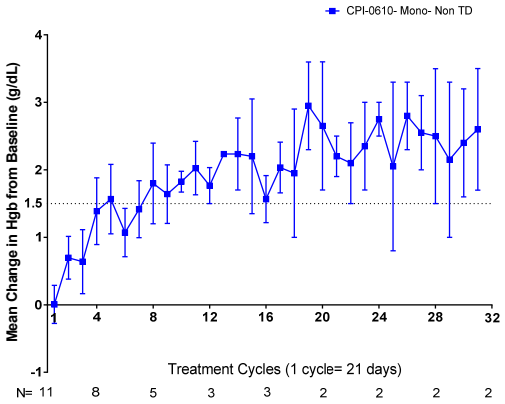
Cohorts 1B and 2B: Hemoglobin Improvement by CPI-0610 Monotherapy

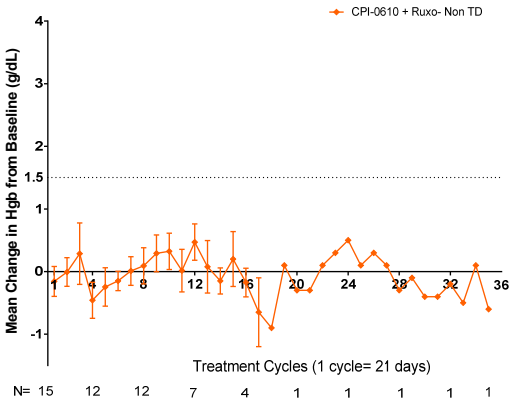
CPI-0610 Monotherapy (n=11)[1]

- 55% (6/11) patients had ≥1.5 g/dL increase in hemoglobin[2]



CPI-0610 + Ruxolitinib (n=15)[1]

- 13% (2/15) patients had ≥1.5 g/dL increase in hemoglobin[2]



[1] Hemoglobin change in evaluable population: Received treatment for ≥12 weeks
[2] The hemoglobin change from baseline without any transfusion within past 12 weeks
Mean+/-SEM. Preliminary data as of 17 October 2019
Mascarenhas J, et al. ASH 2019. Abstract 670.

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Improvement in Bone Marrow Fibrosis

Treatment Arm	BMF Improvement[1]	BMF Improvement and 1.5 g/dL Hgb↑	BMF Improvement and TD to TI
CPI-0610 Monotherapy	2/9 (22.2%)	2/9 (22.2%)	0/2 (0%)
CPI-0610 Add-on to Ruxolitinib	10/23 (43.5%)	4/23 (17.4%)	4/11 (36.4%)

- 12 of 32 (38%) patients had at least one grade improvement in bone marrow fibrosis
- 10 of 12 (83%) improvements occur within the first six months of treatment

[1] BMF=bone marrow fibrosis. Bone marrow evaluable population: Baseline and at least one post-baseline bone marrow biopsy @ or after 24 weeks available. Data assessed by local labs per the European consensus on grading bone marrow fibrosis and assessment of cellularity (Thiele J, et al. *Haematologica.* 2005;90:1128.)

Hgb↑: 1.5 g/dL hemoglobin increase from baseline. Received treatment for ≥12 weeks; mean+/-SEM. The increases in hemoglobin were confirmed within 6 weeks

Preliminary data as of 17 October 2019

Mascarenhas J, et al. ASH 2019. Abstract 670.

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Results from a Phase 2 Study of Navitoclax in Combination with Ruxolitinib in Patients with Primary or Secondary Myelofibrosis

ASH 2019 Abstract 671

Claire N Harrison, Professor, Jacqueline S Garcia, MD, Ruben A Mesa, MD, Tim CP Somervaille, MD, PhD, Rami S. Komrokji, MD, Naveen Pemmaraju, MD, Catriona Jamieson, MD, PhD, Nikolaos Papadantonakis, MD, PhD, MSc, James M. Foran, MD, Casey L. O'Connell, MD, Leanne Holes, BS, MBA,, Jia , PhD, MBA, Jason Harb, PhD, Jessica Hutti, PhD and Josef T. Prchal, MD

Harrison CN, et al. ASH 2019. Abstract 671.

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Navitoclax Combined with Ruxolitinib: Study Design

Study design:	▪ Phase 2 single-arm, multicenter, open-label study assessed the efficacy and safety of navitoclax combined with ruxolitinib in patients with MF
Inclusion criteria:	▪ Diagnosis of PMF or secondary MF, ECOG 0–2, received at least 12 weeks of continuous ruxolitinib therapy prior to study treatment initiation
Methods:	▪ Patients received a starting dose of 50 mg navitoclax once-daily combined with the current stable dose of ruxolitinib (≥10 mg BID) ▪ Weekly intra-patient dose-escalation of navitoclax was allowed to a maximum daily dose of 300 mg based on tolerability and platelet count. ▪ Treatment continued until the end of clinical benefit, unacceptable toxicity, or discontinuation

Harrison CN, et al. ASH 2019. Abstract 671.

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Results

Patient Characteristics

Measure	Patients (N=34)
Median duration of prior ruxolitinib therapy, days	745
≥3 lines of prior therapy, n	9
Mean baseline platelet count	231 X 10^9/L
Mean baseline Hgb	10. g/dL
Presence of *JAK2* mutations, n	27
Presence of *CALR* mutations, n	7
High molecular risk disease, n	17

- Maximal navitoclax dose of 300 mg was achieved in 23 patients
- Of the 25 (74%) patients that enrolled on ruxolitinib doses >10 mg BID, 22 (88%) subsequently had the dose of ruxolitinib reduced to 10 mg BID

Efficacy Findings

Measure	Evaluable Patients (N=24)
Completed ≥24 weeks on study, n	20
Discontinued prior to week 24, n	4
Achieved SVR24 from baseline, n (%)	7 (29)
Reductions in in driver mutation burden >5%, n (%)	10 (42)
BMF improvement ≥grade, n (%)	6 (25)

- Median TSS was 7.4, a 20% improvement from baseline
- A SVR35 at any time on study was achieved in 10 patients (42%)

Harrison CN, et al. ASH 2019. Abstract 671.

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A Phase 2 Study of Luspatercept in Patients With Myelofibrosis-Associated Anemia

ASH 2019 Abstract 557

Aaron T. Gerds, Alessandro M. Vannucchi, Francesco Passamonti, Marina Kremyanskaya, Jason Gotlib, Jeanne M. Palmer, Kelly McCaul, Vincent Ribrag, Adam J. Mead, Claire Harrison, Ruben Mesa, Jean-Jacques Kiladjian, Giovanni Barosi, Robert Peter Gale, Abderrahmane Laadem, Joseph Pariseau, Torsten G. Gerike, Jennie Zhang, Peter G. Linde, Joseph G. Reynolds, Srdan Verstovsek

Gerds AT, et al. ASH 2019. Abstract 557.

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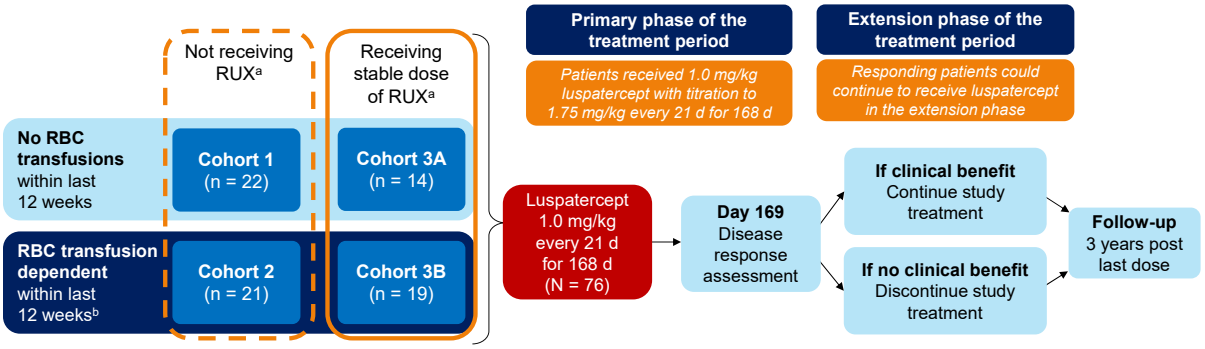
Study Design



- **No RBC Transfusion Cohorts 1 and 3A**
  - No RBC transfusions within 12 weeks before enrollment
  - Hb levels ≤9.5 g/dL (recorded on three separate occasions)
- **RBC Transfusion Cohorts 2 and 3B**
  - RBC transfusion dependent (2–4 RBC U/28 d within 12 weeks before enrollment)
  - No transfusion-free interval >6 weeks

[a] A stable daily dose of ruxolitinib for at least 16 weeks at enrollment. [b] 2–4 RBC U/28 d transfused within last 12 weeks.
Gerds AT, et al. ASH 2019. Abstract 557.

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Efficacy Results

Response Characteristic	No RBC Transfusions[a]		RBC Transfusion Dependent[a]	
	Not Receiving RUX[b]	Receiving RUX[b]	Not Receiving RUX[b]	Receiving RUX[b]
	Cohort 1 (n = 22)	Cohort 3A (n = 14)	Cohort 2 (n = 21)	Cohort 3B (n = 19)
Hb increase ≥1.5 g/dL from baseline for ≥12 consecutive weeks[c,d]				
Hb increase ≥1.5 g/dL at every assessment	3 (14)	3 (21)	–	–
Mean Hb increase ≥1.5 g/dL	4 (18)	9 (64)	–	–
RBC transfusion-free ≥12 consecutive weeks, n (%)[e]	**–**	**–**	**2 (10)**	**6 (32)**
Duration of response, median (range), weeks[f]	–	–	32 (16–49)	39 (12–77)
≥50% reduction in RBC transfusion burden from baseline, n (%)[g]	**–**	**–**	**8 (38)**	**10 (53)**

- The median duration of luspatercept treatment was 24 weeks (range 2–86 weeks)
- Dose escalation to 1.33 mg/kg and 1.75 mg/kg, was observed in 65 (86%) and 50 (66%) patients
- RUX daily dose remained stable throughout the 24-week treatment period in both cohorts 3A and 3B
- 19 (25%) patients remain on study

[a] In the 12 weeks prior to treatment. [b] A stable daily dose of ruxolitinib for ≤16 weeks at enrollment. [c] Per central laboratory assessment. [d] Three subjects have an ongoing response at the time of data cutoff. [e] Six subjects have an ongoing response at the time of data cutoff. [f] Duration of response was defined as the duration of the longest single response period. [g] Minimum four RBC U decrease.

Gerds AT, et al. ASH 2019. Abstract 557.