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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

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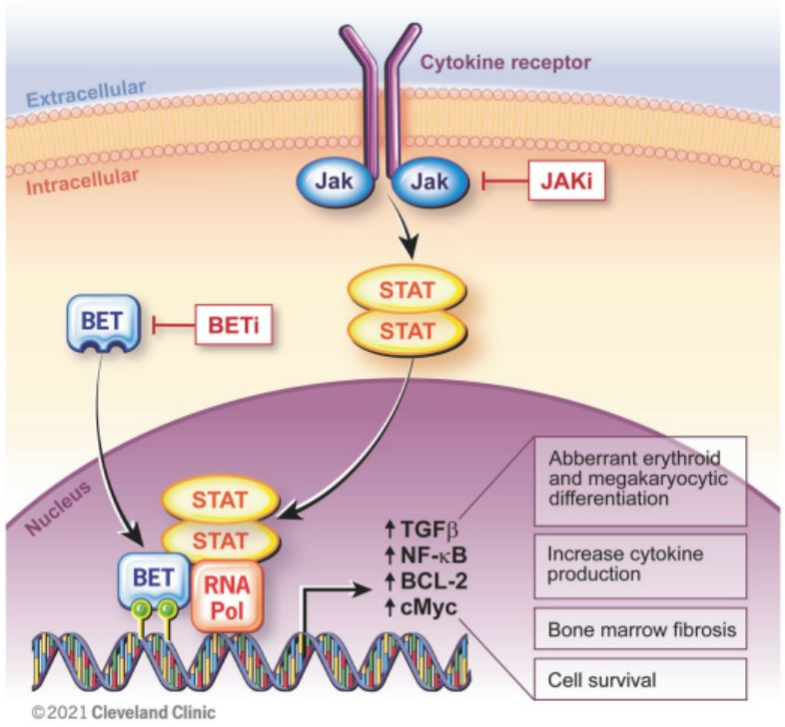
- Attending meetings or advisory boards: Abbvie, AOP Health, CTI Biopharma Galecto, Geron, Promedior and Roche
- Leadership role: EHA, MPN Voice

Combination of BET and JAK inhibition



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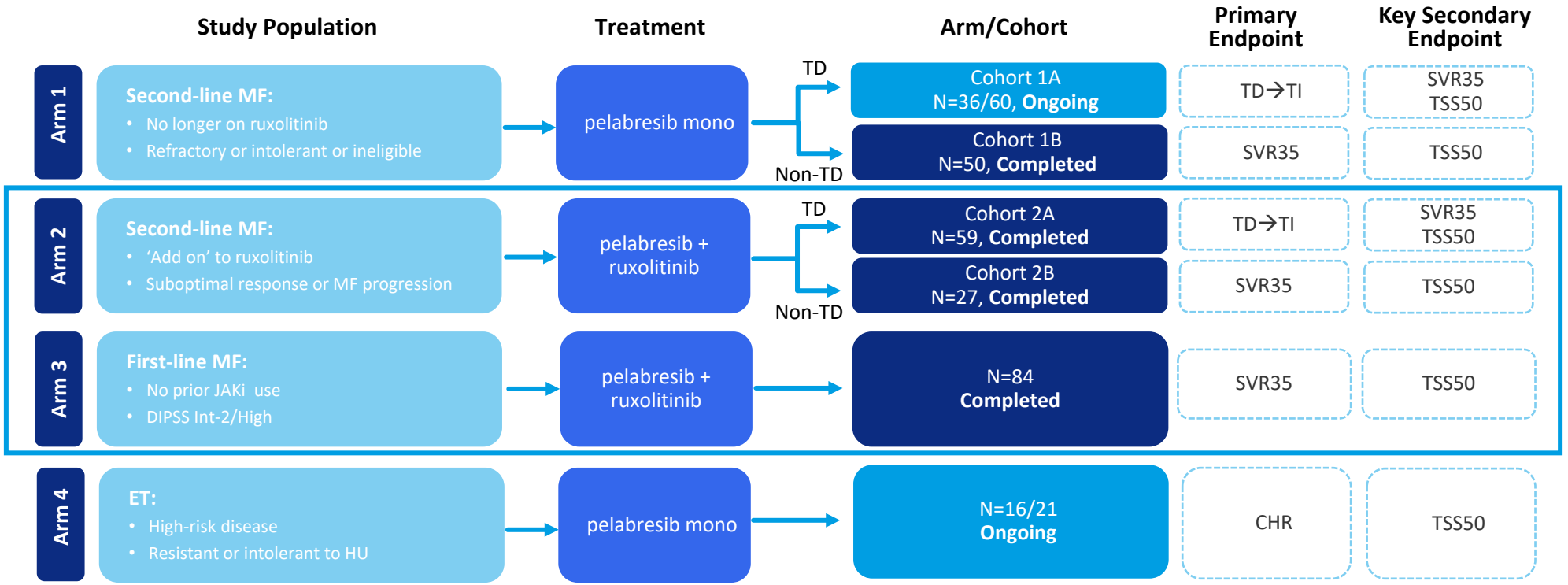
- JAK inhibition with ruxolitinib is standard of care in patients not eligible for HSCT
- Unmet medical need persists due to high discontinuation rates as a result of toxicities or limited efficacy of JAK inhibitors[1]
- Pelabresib, a BET inhibitor, downregulates the expression of genes that contribute to the heterogenous pathology of myelofibrosis[2–6]
- Preclinical data shows synergistic effect of BET and JAK inhibition in myelofibrosis[7]

BCL-2, B-cell lymphoma 2; BET, bromodomain and extraterminal domain; BETi, BET inhibitor; c-Myc, cellular Myc; HSCT, hematopoietic stem cell transplant; JAK, Janus kinase; JAKi, JAK inhibitor; MF, myelofibrosis; NF-κB, nuclear factor kappa B; RNA pol, ribonucleic acid polymerase; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor β.

1. Verstovsek S, et al. *Haematologica* 2015;100:479–488; 2. Stratton MS, et al. *F1000Res* 2017;6:F1000 Faculty Rev–1015; 3. Ding N, et al. *PNAS* 2015;112:15713–15718; 4. Ceribelli M, et al. *PNAS* 2014;111:11365–11370; 5. Tefferi A, et al. *J Clin Oncol* 2011;29:573–582; 6. Keller P, et al. *Hemasphere* 2021;5(Suppl 2):515; 7. Kleppe M, et al. *Cancer Cell* 2018;33:29–43.e7.

MANIFEST is an ongoing, global, open-label Phase 2 study investigating pelabresib in MF and ET



MANIFEST study: NCT02158858.

CHR, complete hematologic response; DIPSS, Dynamic International Prognostic Scoring System; ET; essential thrombocythemia; HU, hydroxyurea; Int-2, Intermediate-2; JAK, Janus kinase; JAKi, JAK inhibitor; MF, myelofibrosis; SVR35, ≥35% reduction in spleen volume at Week 24; TD, transfusion dependent; TI, transfusion independent; TSS50, ≥50% reduction in total symptom score at Week 24.

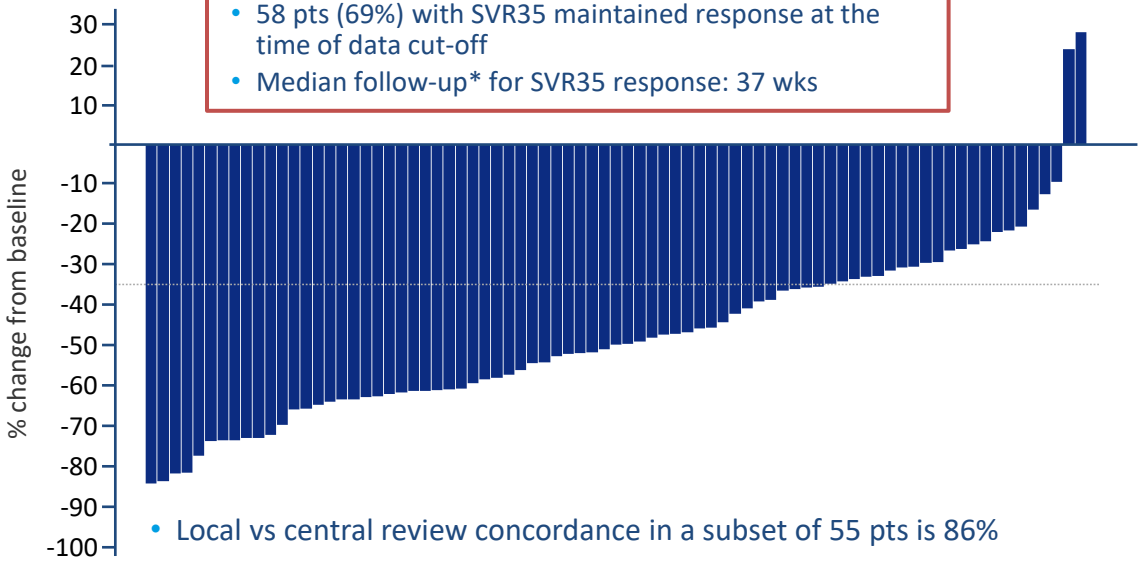
Baseline demographics and disease characteristics

Characteristic		Arm 3 (N=84)	Arm 2 (N=86)
Age (years)	Mean (SD)	67 (10)	68 (9)
Gender	Male, n (%)	59 (70)	55 (64)
DIPSS*	Int-1, n (%)	20 (24)	7 (8)
	Int-2, n (%)	51 (61)	55 (64)
	High, n (%)	13 (16)	24 (28)
MF subtype	pMF, pPV, pET n (%)	46 (55), 9(11), 26 (31)	57 (66), 11 (13), 16 (19)
Hemoglobin (g/dL)	Median (min, max)	9 (7, 17)	9 (6, 13)
	<10, n (%)	55 (66)	68 (79)
Platelet (× 10^9/L)	Median (min, max)	293 (100, 1849)	167 (70, 1114)
	≤200, n (%)	29 (35)	53 (62)
Spleen volume (cc)	Median (min, max)	1698 (458, 4782)	2046 (121, 8489)
TSS	Median (min, max)	16 (0, 38)	19 (1, 62)
Mutations	HMR,† n (%)	47 (56)	52 (61)
	ASXL1, n (%)	37 (44)	44 (51)
	JAK2 V617F, n (%)	59 (70)	48 (56)
	CALR, n (%)	17 (20)	17 (20)
	MPL, n (%)	6 (7)	7 (8)
	Triple negative, n (%)	3 (4)	12 (14)
Ruxolitinib dose on C1D1 (mg, total daily)	Median (min, max)	30 (10, 40)	20 (10, 50)

*IPSS: Arm 3: 13% Int-1, 33% Int-2, 53% High; Arm 2: 4% Int-1, 21% Int-2, 76% High; †HMR: *ASXL1, EZH2, IDH1/2, SRSF2, U2AF1.*
C1D1, Cycle 1, Day 1; DIPSS, Dynamic International Prognostic Scoring System; HMR, high-molecular risk mutation; Int, Intermediate; IPSS, International Prognostic Scoring System; MF, myelofibrosis; pMF, primary MF; pET, post-essential thrombocythemia; pPV, post-polycytemia vera; SD, standard deviation; TSS, total symptom score.

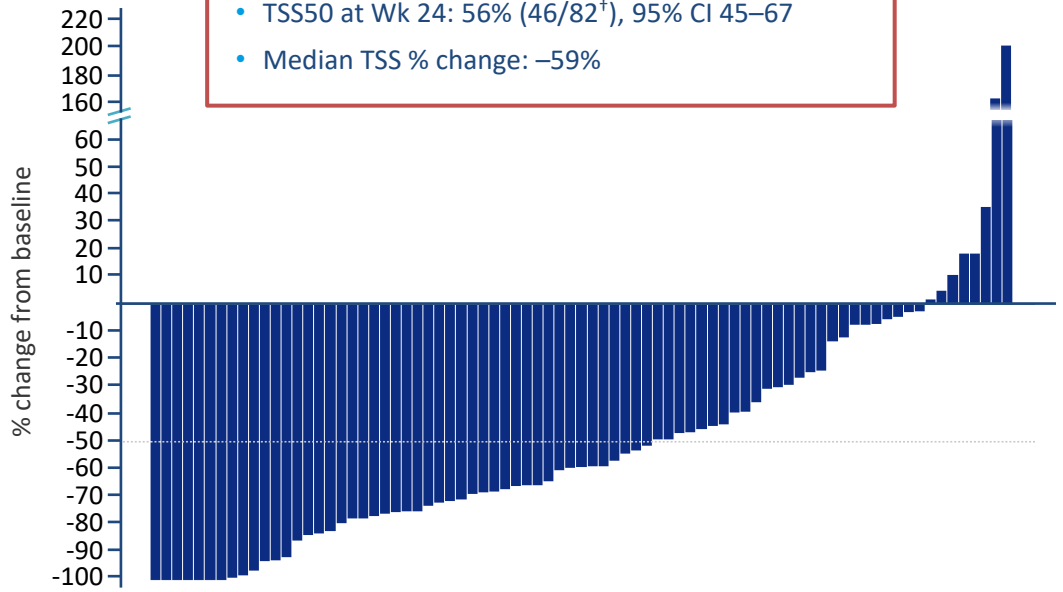
Arm 3: JAKi-naïve MF patients — Reduction of spleen volume and total symptom score in majority of the patients

- 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



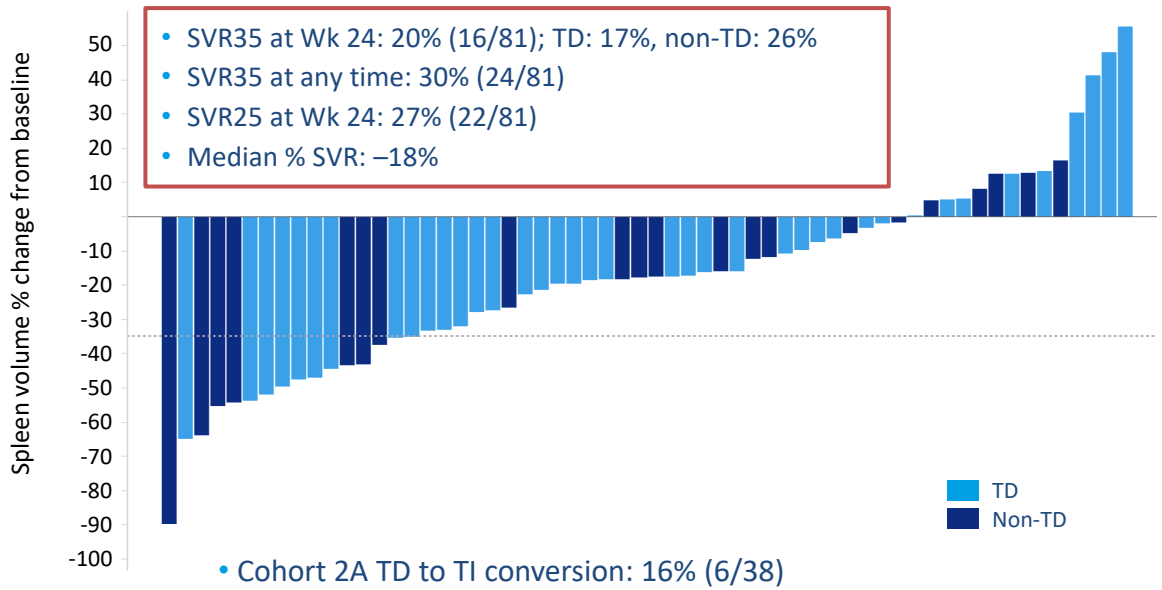
- Local vs central review concordance in a subset of 55 pts is 86%

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

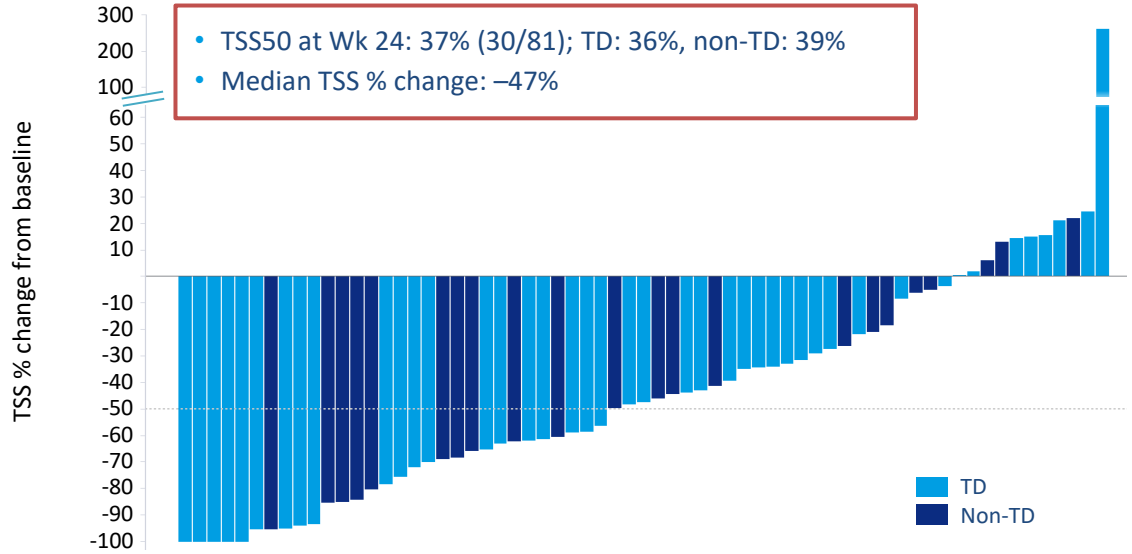


SVR per local radiology review; central radiology review is ongoing.
Patients are evaluable for SVR35 or TSS50 at Wk 24 if they have had Wk 24 assessment by the data cut-off date or discontinued without Wk 24 assessment at any time.
*Reverse Kaplan–Meier estimate of median duration of follow-up for SVR35 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.

Arm 2: MF patients with suboptimal response to ruxolitinib — Reduction of spleen volume and total symptom score in most of the patients



- SVR35 at Wk 24: 20% (16/81); TD: 17%, non-TD: 26%
- SVR35 at any time: 30% (24/81)
- SVR25 at Wk 24: 27% (22/81)
- Median % SVR: –18%



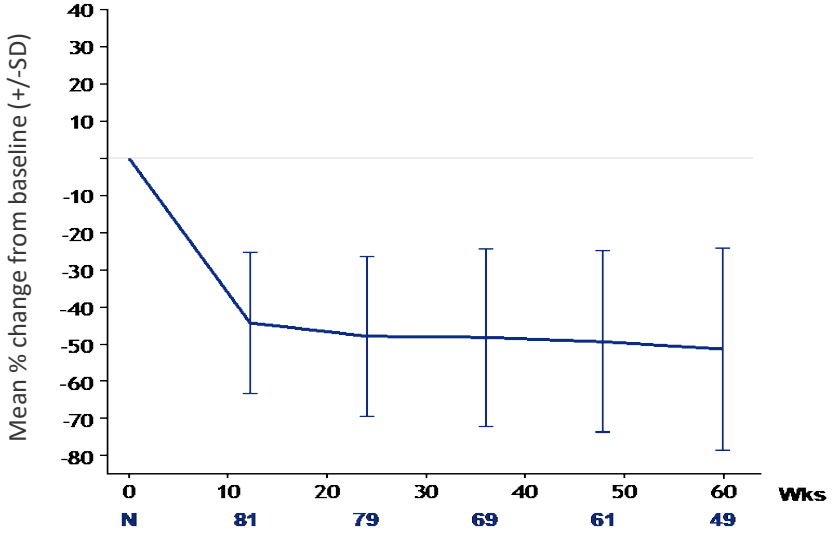
- TSS50 at Wk 24: 37% (30/81); TD: 36%, non-TD: 39%
- Median TSS % change: –47%

- Cohort 2A TD to TI conversion: 16% (6/38)
- Cohort 2B Hgb response:* 22% (6/27)

Five pts nonevaluable for SVR35 or TSS50: 2 pts due to missing baseline, and 3 ongoing pts did not reach Wk 24 at data cut-off.
*Hgb response, defined as postbaseline mean Hgb increase of at least 1.5g/dL, is required for any 12 wks RBC transfusion-free period.
Hgb, hemoglobin; MF, myelofibrosis; pts, patients; RBC, red blood cell; SVR, spleen volume reduction; SVR25, ≥25% reduction in spleen volume from baseline; SVR35, ≥35% reduction in spleen volume from baseline; TD, transfusion dependent; TI, transfusion independent; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline; wk, week.

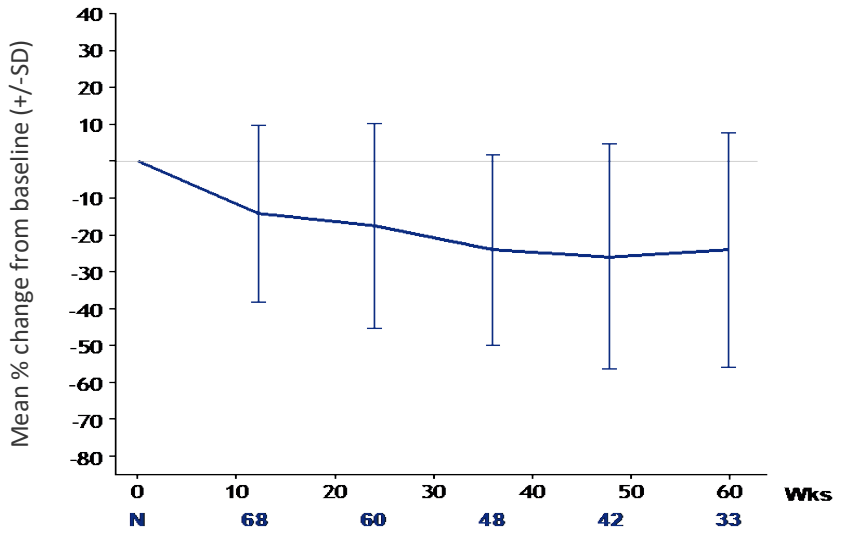
Deepening and durable spleen volume reduction over time in JAKi-naïve MF patients and MF patients with suboptimal response to ruxolitinib

Arm 3: Pelabresib in combination with ruxolitinib in JAKi treatment-naïve MF patients



Median treatment duration (95% CI):* NR (19.2 mo–NR)
Median follow-up time (95% CI):‡ 21.8 mo (21.2–22.5)

Arm 2: Pelabresib add-on to ruxolitinib in MF patients with inadequate response to ruxolitinib



Median treatment duration (95% CI):† 14.0 mo (8.4–20.6)
Median follow-up time (95% CI):‡ 24.4 mo (23.0–30.7)

*NR: Not reached based on a Kaplan–Meier analysis. 63% of patients were still ongoing at the time of data cut-off.
†Kaplan–Meier estimate (ongoing patients censored). 32% of patients were still ongoing at the time of the data cut-off.
‡Reverse Kaplan–Meier estimate of treatment duration.
CI, confidence interval; JAKi, Janus kinase inhibitor; MF, myelofibrosis, mo, months, NR, not reached; SD, standard deviation; wks, weeks.

Arm 3: JAKi-naïve MF patients — Summary of AEs

TEAEs of all grades that occurred in ≥20% of pts	All Grade N=84* n (%)	Grade 3 N=84* n (%)	Grade 4 N=84* n (%)
Hematologic Events			
Anemia	35 (42%)	28 (33%)	1 (1%)
Thrombocytopenia†	44 (52%)	7 (8%)	3 (4%)
Nonhematologic Events			
GI Events			
Diarrhea	29 (35%)	1 (1%)	0
Constipation	21 (25%)	0	0
Nausea	20 (24%)	0	0
Abdominal pain‡	19 (23%)	0	0
Other Nonhematologic Events			
Asthenic conditions§	28 (33%)	1 (1%)	0
Musculoskeletal pain¶	25 (30%)	0	0
Respiratory tract infection**	24 (29%)	3 (4%)	3 (4%)
Dizziness††	22 (26%)	0	0
Dysgeusia	18 (21%)	0	0
Dyspnea	17 (20%)	4 (5%)	0

- Serious adverse events reported in ≥3 pts were respiratory tract infections (6 pts), pyrexia (3 pts)
- 7 pts (8%) reported TEAEs that led to pelabresib discontinuation
- GI events were mostly low grade and manageable. Median time to GI events were 16 wks
- 5 Grade 5 TEAEs were reported:
  - COVID-19 (1 pt), MOF due to sepsis secondary to infections (bacterial endocarditis and pneumonia) and acute respiratory distress syndrome due to ruxolitinib withdrawal (2 pts each)
  - All were assessed by PI as not related to pelabresib except MOF due to sepsis secondary to pneumonia

*Safety-evaluable population: Received at least one dose of study drug at the time of the data cut; †Includes TEAE platelet count decrease; ‡Includes TEAE abdominal pain upper; §Includes TEAEs of asthenia, fatigue; ¶Includes TEAEs of myalgia, arthralgia and malaise; **Includes TEAEs of upper respiratory tract infection, influenza, bronchitis, sinusitis, rhinitis, nasopharyngitis, pneumonia, COVID-19 and COVID-19 pneumonia; ††Includes TEAE vertigo.
AE, adverse event; GI, gastrointestinal; JAKi, Janus kinase inhibitor; MF, myelofibrosis, MOF, multiorgan failure; PI, principal investigator; pt, patient; TEAE, treatment-emergent adverse event; wks, weeks.

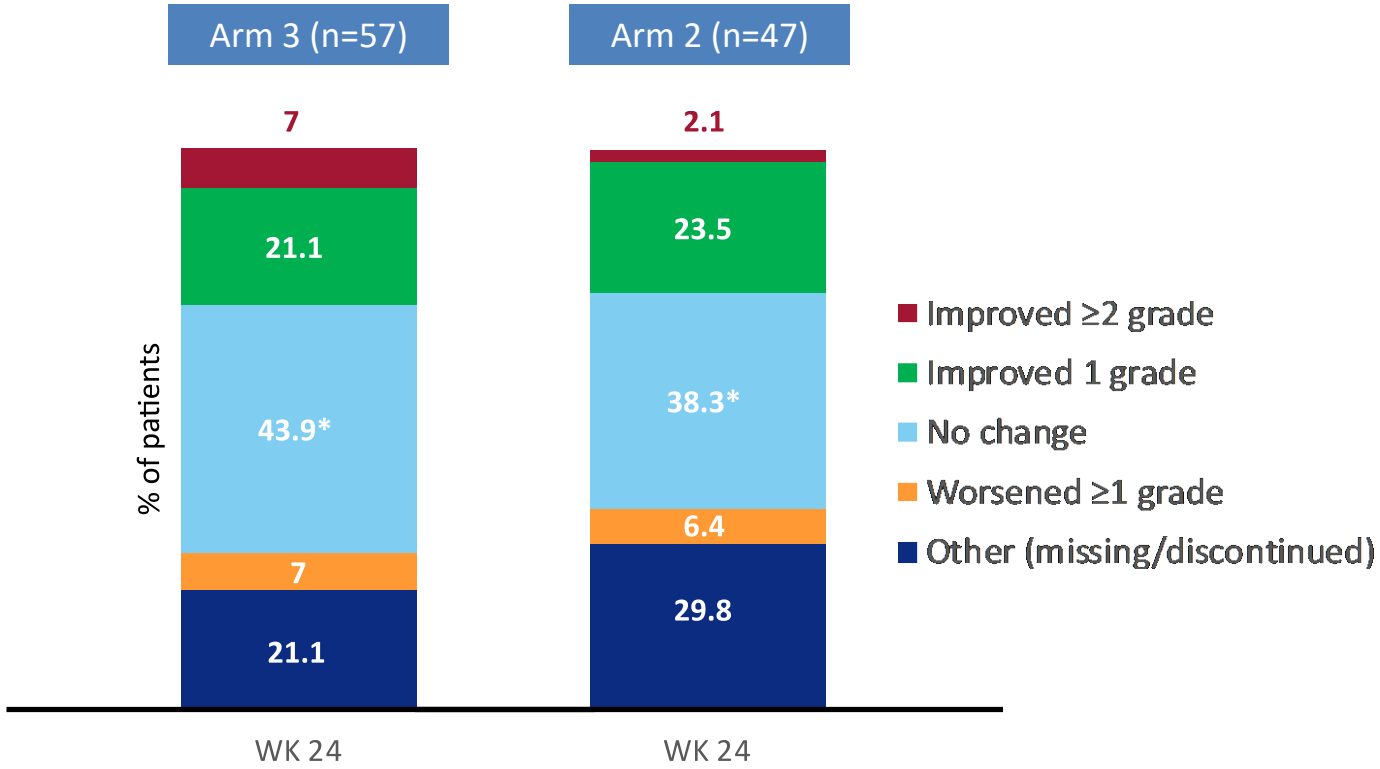
Arm 2: MF patients with suboptimal response to ruxolitinib — Summary of AEs

TEAEs of all grades that occurred in ≥20% of pts	All Grade N=86* n (%)	Grade 3 N=86* n (%)	Grade 4 N=86* n (%)
Hematologic Events			
Thrombocytopenia†	45 (52%)	23 (27%)	5 (6%)
Anemia	23 (27%)	14 (16%)	2 (2%)
Nonhematologic Events			
GI Events			
Diarrhea	47 (55%)	3 (4%)	0
Nausea	33 (38%)	2 (2%)	0
Abdominal pain‡	19 (22%)	3 (4%)	0
Other Nonhematologic Events			
Asthenic conditions§	33 (38%)	4 (5%)	0
Respiratory tract infection¶	29 (34%)	5 (6%)	0
Cough	23 (27%)	0	0
Dysgeusia	22 (26%)	0	0
Bruising**	19 (22%)	0	0
Appetite decrease	19 (22%)	1 (1%)	0
Dizziness††	18 (21%)	0	0
Musculoskeletal pain‡‡	18 (21%)	0	0

- Serious adverse events reported in ≥3 pts were anemia (6 pts), RTIs (4 pts) and UTIs (3 pts)
- 20 pts (23%) reported TEAEs that led to pelabresib discontinuation
- 7 Grade 5 TEAEs were reported:
  - Acute kidney injury, traumatic subdural hematoma (mechanical fall), brain stem hemorrhage (no concomitant thrombocytopenia), disease progression, transformation to AML, congestive heart failure, suspected lung cancer
  - All were assessed by PI as not related to pelabresib except acute kidney injury

*Safety-evaluable population: Received at least one dose of study drug as of the data cut; †Includes TEAE platelet count decrease; ‡Includes TEAE abdominal pain upper, abdominal pain lower; §Include TEAEs of asthenia, fatigue, lethargy and malaise; ¶Includes TEAEs of upper RTI, lower RTI, bronchitis, tracheitis, sinusitis, rhinitis, nasopharyngitis, pneumonia and COVID-19; **Include TEAEs of contusion, ecchymosis and increased tendency to bruise; ††Include TEAEs of vertigo, balance disorder; ‡‡Include TEAEs of arthralgia, myalgia.
AE, adverse event; AML, acute myeloid leukemia; GI, gastrointestinal; MF, myelofibrosis, PI, principal investigator; pts, patients; RTI, respiratory tract infection; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

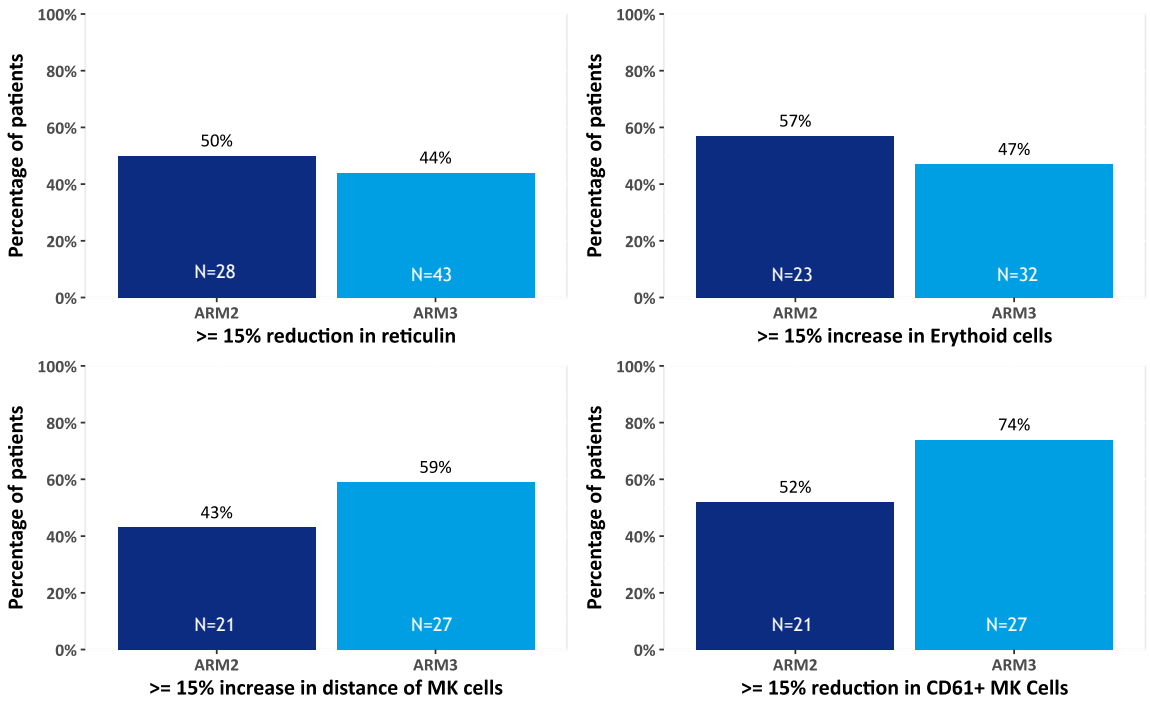
Improvements in bone marrow fibrosis grade after 24 wks of treatment by central pathology review



- 28% (Arm 3) and 26% (Arm 2) achieved ≥1 grade improvement at Wk 24
  - 56% (Arm 3) and 50% (Arm 2) of patients maintained the improvement at the next available assessment or longer
- 40% (Arm 3) and 39% (Arm 2) achieved ≥1 grade improvement at anytime (best response)

Patients evaluable if nonmissing baseline or discontinued without Wk 24 bone marrow assessment; Bone marrow fibrosis grade assessed by three independent and blinded pathologists per central pathology review, maturing data with central review ongoing.
*56.0% (Wk 24) in Arm 3 and 83.3% (Wk 24) in Arm 2 of the category 'no change' had Grade 3 at baseline, and no further worsening would have been detectable. Wk, week.

Improvements in bone marrow fibrosis, increase in erythroid cells and decrease in megakaryocyte clusters after 24 wk of treatment



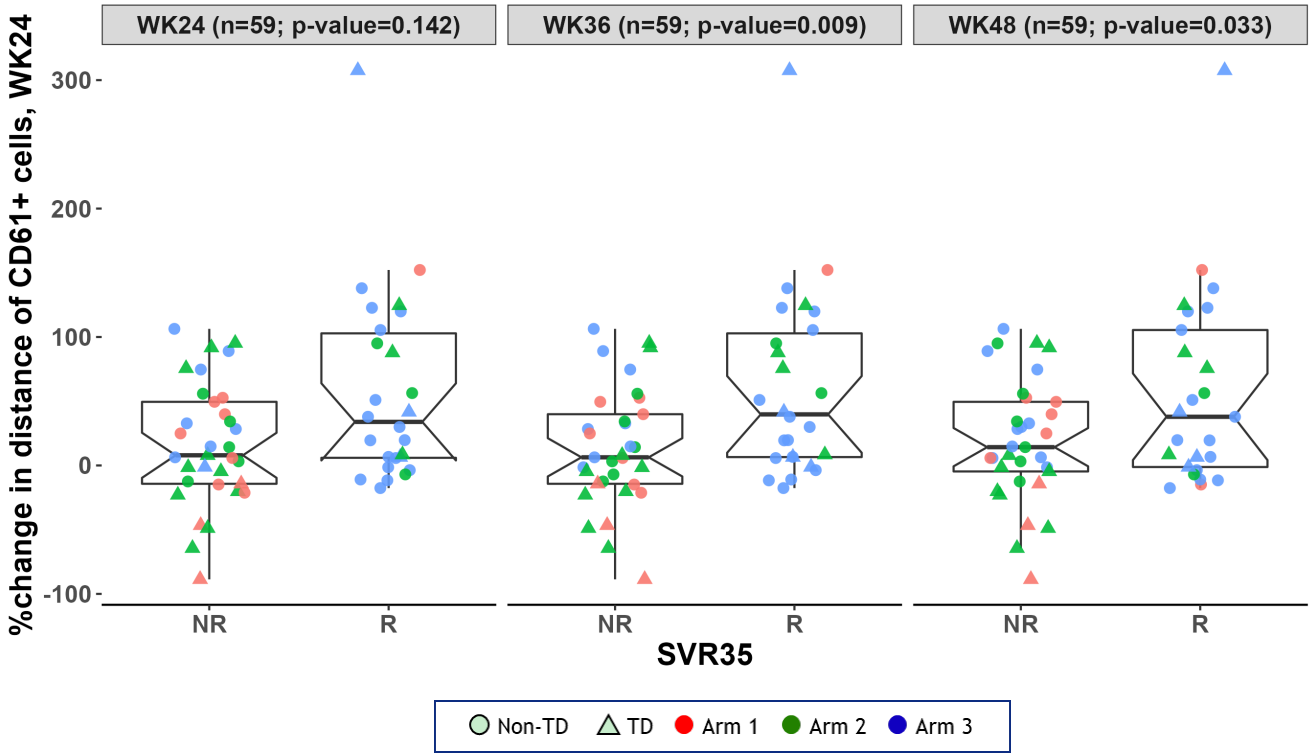
- Bone marrow improvement is quantified by decrease in megakaryocyte clusters, reduced reticulin density and increase in erythrocytes

N: total number of patients with paired baseline and Wk 24 bone marrow biopsies evaluated for reticulin, CD71 and CD61 staining.
CD61, platelet glycoprotein IIIa; CD71, transferrin receptor; H&E, hematoxylin and eosin stain; MK, megakaryocyte; wk, week.

Slide pairs were stained centrally for H&E, reticulin, CD71 and CD61; scanned and digital images were evaluated for the following markers:
- Reticulin density: mean number of intersections from up to 10 randomly selected 400 mm^2 fields per image
- CD71 (erythrocyte marker): % CD71+ stained cells/total cell count for whole image
- CD61 density (megakaryocyte marker): mean number of megakaryocytes from up to 10 randomly selected 400 mm^2 fields per image
- CD61 distance: mean distance between nuclei in a field with variable number of nuclei and up to 10 fields per image; QC review of each slide. Each 400 mm^2 field must pass QC criteria

A 15% threshold for improvement was selected based on the median value of % change in reticulin intersections across the entire population analyzed.
The difference in total number of patients analyzed for each marker reflects the number of biopsies and images that did not fail QC criteria.

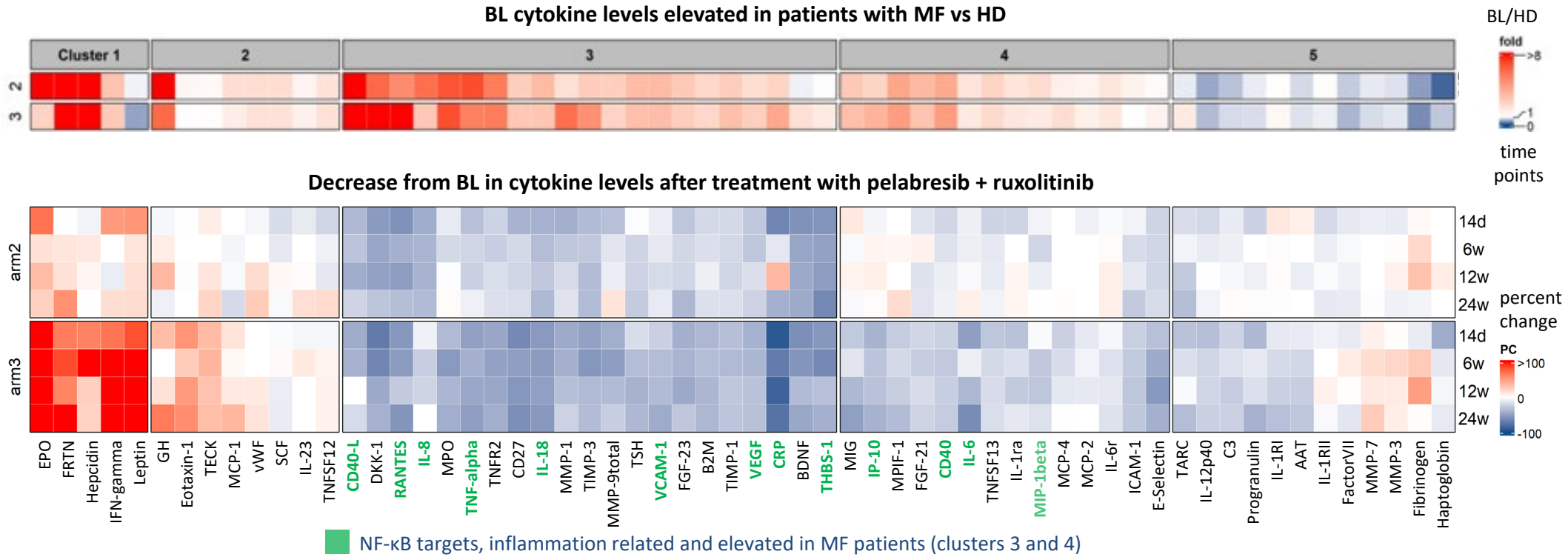
Megakaryocyte ‘de-clustering’ in bone marrow correlated with SVR35 response



P-values were computed by logistic regression with age and gender adjustment.
CD61, platelet glycoprotein IIIa; NR, not reached; R, reached; SVR35, ≥35% reduction in spleen volume at Week 24; TD, transfusion-dependent; wk, week.

Decreased plasma levels of MF-associated/inflammation-related cytokines in Arm 2 and 3 patients

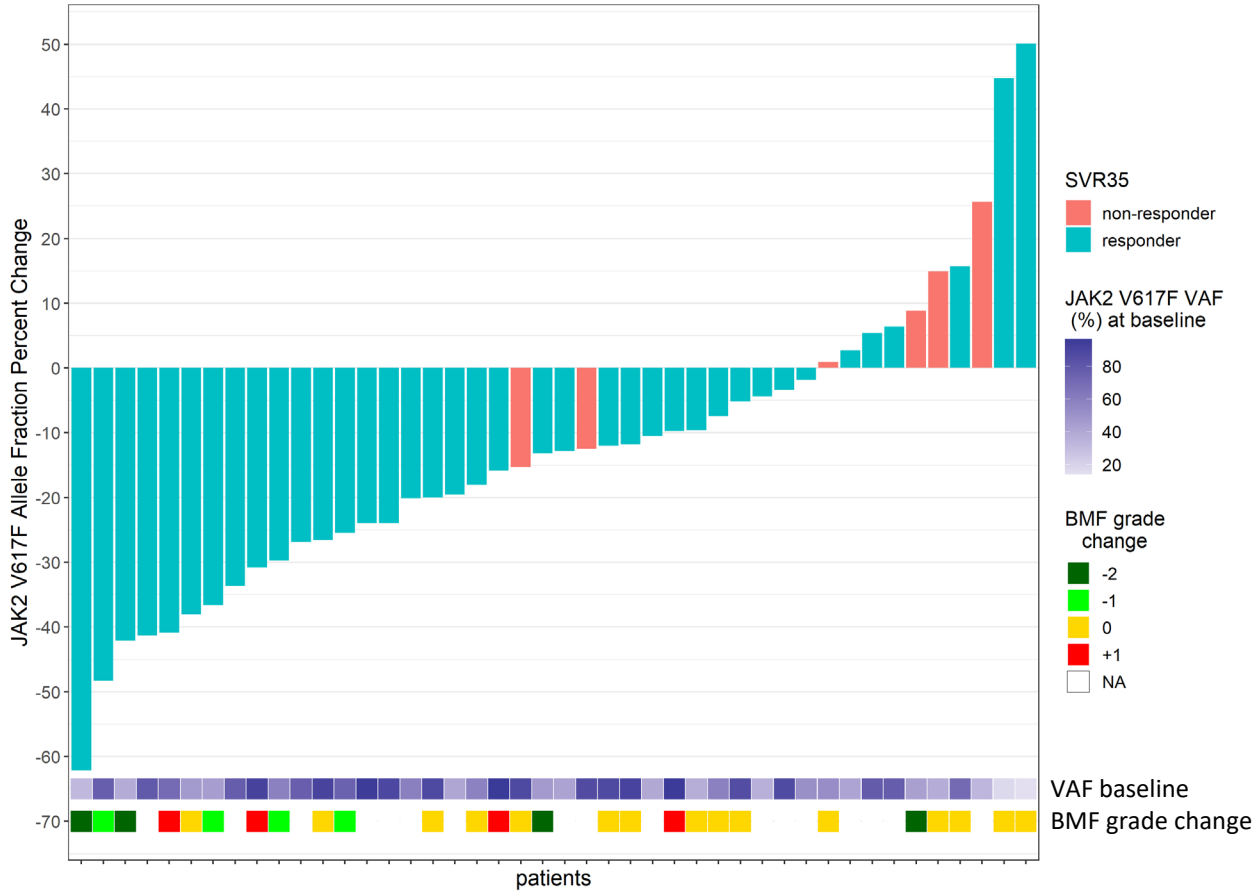
Cytokines previously shown to be NF-κB targets, inflammation related and elevated in MF patients (clusters 3 and 4) are strongly decreased during treatment. Downregulation was rapid (14 days) and durable (through 24 weeks)



BL, baseline; d, day; HD, healthy donors; MF, myelofibrosis; NF-κB, nuclear factor kappa B; w, week.

Reduction of *JAK2* VAF and BM fibrosis observed with pelabresib and ruxolitinib combination treatment in JAKi-naïve Arm 3 patients

*JAK2*V617F VAF Change, SVR35 and Bone Marrow Fibrosis Grade Change at Week 24



BM, bone marrow; BMF, BM fibrosis; *JAK2,* Janus kinase 2 gene; JAKi, JAK inhibitor; NA, not available; SVR35, ≥35% reduction in spleen volume at Week 24; VAF, variant allele frequency.

Conclusions

- Pelabresib in combination with ruxolitinib showed encouraging clinical efficacy with response durability beyond Wk 24 in:
  - JAKi-naïve patients (SVR35 at Wk 24: 68%, SVR35 at any time: 80%, TSS50 at Wk 24: 56%) and
  - Patients with suboptimal response to ruxolitinib (SVR35 at Wk 24: 20%, SVR35 at any time: 30%, TSS50 at Wk 24: 37%)
- The most common treatment-emergent adverse events were low grade
- Decreased plasma levels of several proinflammatory cytokines were observed, and improved bone marrow morphology correlated with SVR

The combination of pelabresib and ruxolitinib was generally well tolerated, and preliminary results showed durable improvements in splenomegaly and symptom burden, with associated biomarker results suggesting potential disease-modifying activity

JAKi, Janus kinase inhibitor; MF, myelofibrosis; SVR, spleen volume reduction; SVR35, ≥35% reduction in spleen volume at Week 24; TSS50, ≥50% reduction in total symptom score at Week 24; wk, week.

Thanks to all the patients, their families and caregivers!

MANIFEST 2

- MANIFEST-2, a Phase 3 randomized double-blind trial of pelabresib + ruxolitinib vs placebo + ruxolitinib in JAKi-naïve MF patient population, has been initiated and is open for enrollment
- https://www.ManifestClinicalTrials.com
- NCT04603495
- Other pelabresib EHA 2022 abstracts: S192, P1029, P1030