Pelabresib (CPI-0610) Combined With Ruxolitinib for JAK Inhibitor Treatment-Naïve Patients With Myelofibrosis: Durability of Response and Safety Beyond Week 24

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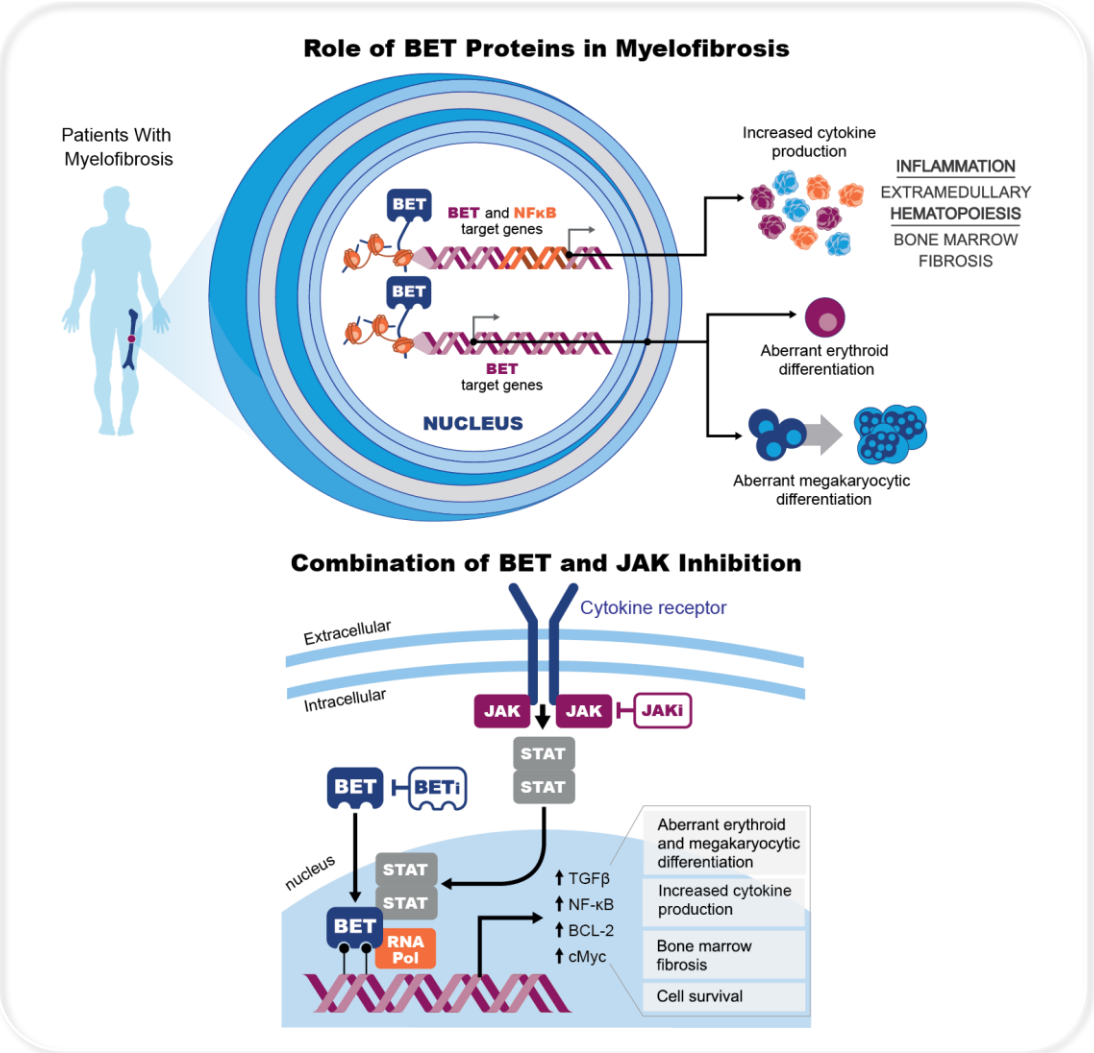
Simultaneous inhibition of BET and JAK in myelofibrosis

A potential therapeutic approach to address heterogenous disease pathology



- JAK inhibition with ruxolitinib is the standard of care in patients with higher risk MF who are ineligible for HSCT, but unmet medical need persists due to limited efficacy with currently available JAKi monotherapy, high rates of discontinuation and toxicities[1]
- Preclinical data indicated synergistic effects of BET and JAK inhibition in MF[2]
- Pelabresib, a BET inhibitor, downregulates the expression of genes that contribute to the heterogenous pathology of MF[3–7]

BET, bromodomain and extraterminal domain; JAK, Janus kinase; NF-κB, nuclear factor kappa B; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor β.

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

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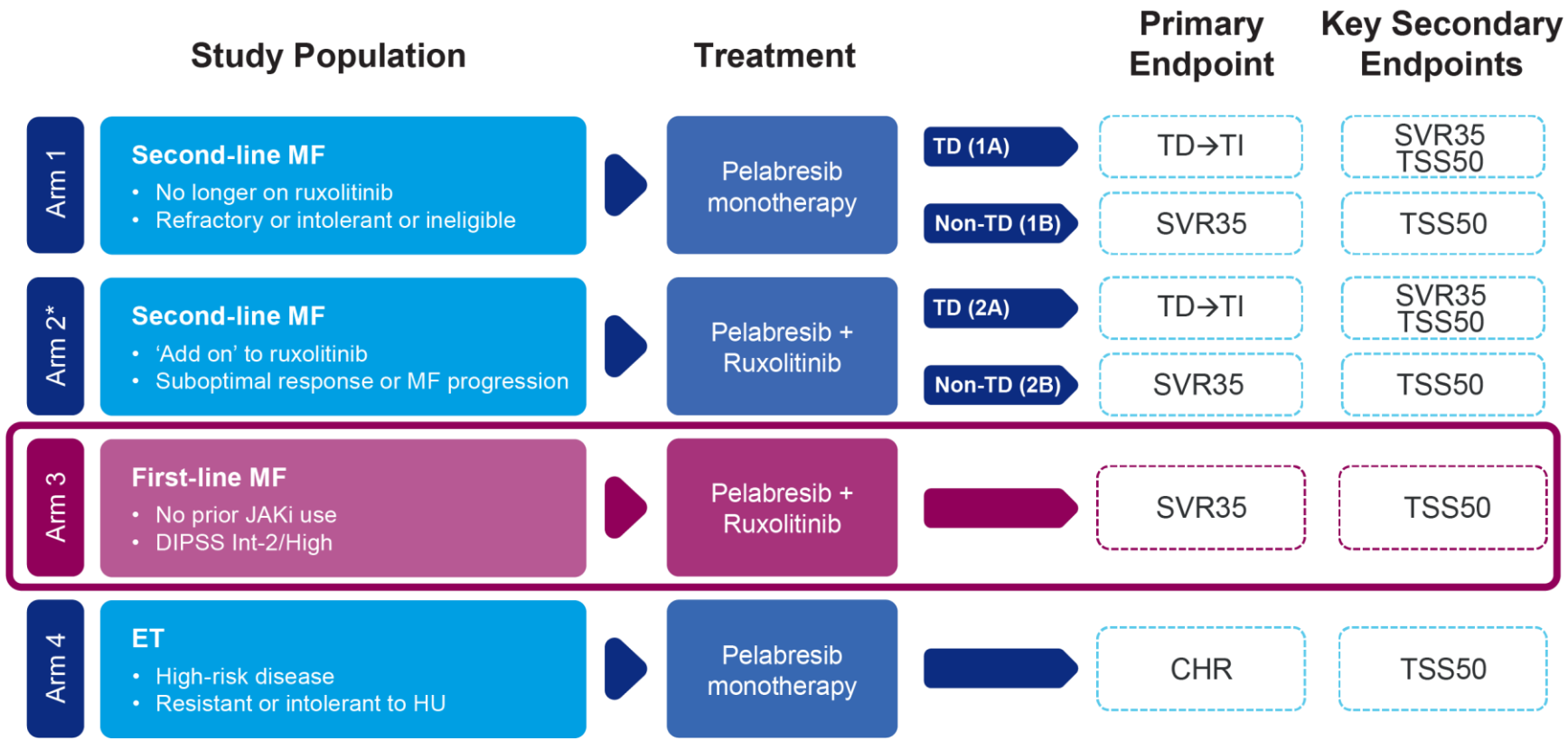
Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

MANIFEST: Ongoing, global, open-label Phase 2 study investigating pelabresib in myelofibrosis and essential thrombocythemia



**Pelabresib (CPI-0610) as Add-on to Ruxolitinib in Myelofibrosis: Durability of Response and Safety Beyond Week 24 in the Phase 2 MANIFEST Study* — Harrison C, et al. Poster presentation 4344, Dec 12, 6:00–8:00 pm EST

CHR, complete hematologic response; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; HU, hydroxyurea; Int-2, intermediate-2; JAKi, Janus kinase inhibitor; 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.

Clinicaltrials.gov. NCT02158858. Available at: https://clinicaltrials.gov/ct2/show/NCT02158858. Accessed November 10, 2022.

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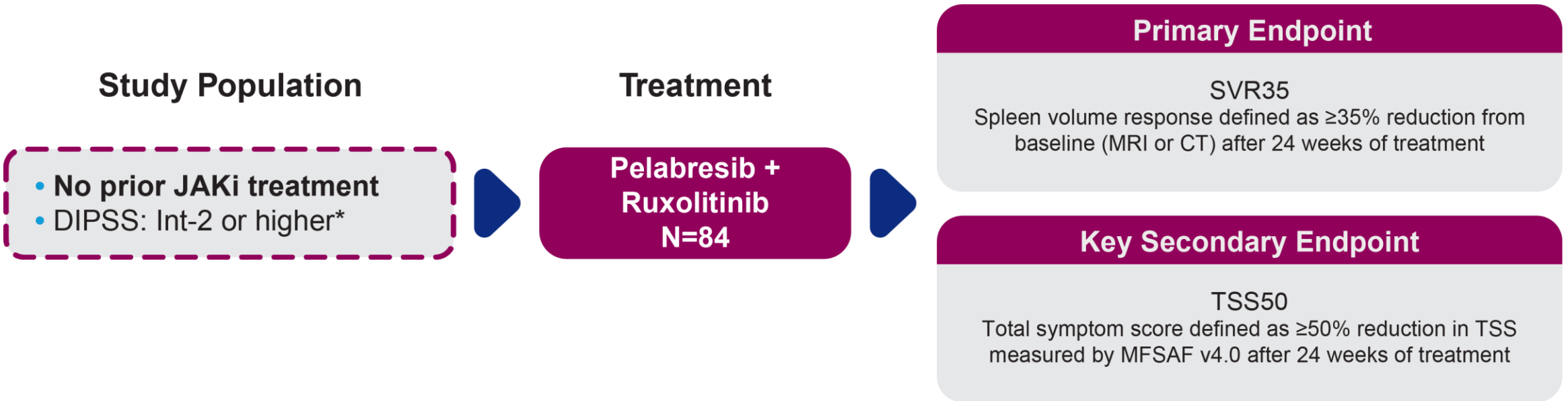
MANIFEST Arm 3: Pelabresib + ruxolitinib in JAKi-naïve myelofibrosis patients



*Patients with DIPSS Int-1 were allowed to enroll prior to the protocol amendment.
CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; Int, intermediate; JAKi, Janus kinase inhibitor; MFSAF, Myelofibrosis Symptom Assessment Form; SVR35, ≥35% reduction in spleen volume from baseline; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline.
Clinicaltrials.gov: NCT02158858. Available at: https://clinicaltrials.gov/ct2/show/NCT02158858. Accessed November 10, 2022.

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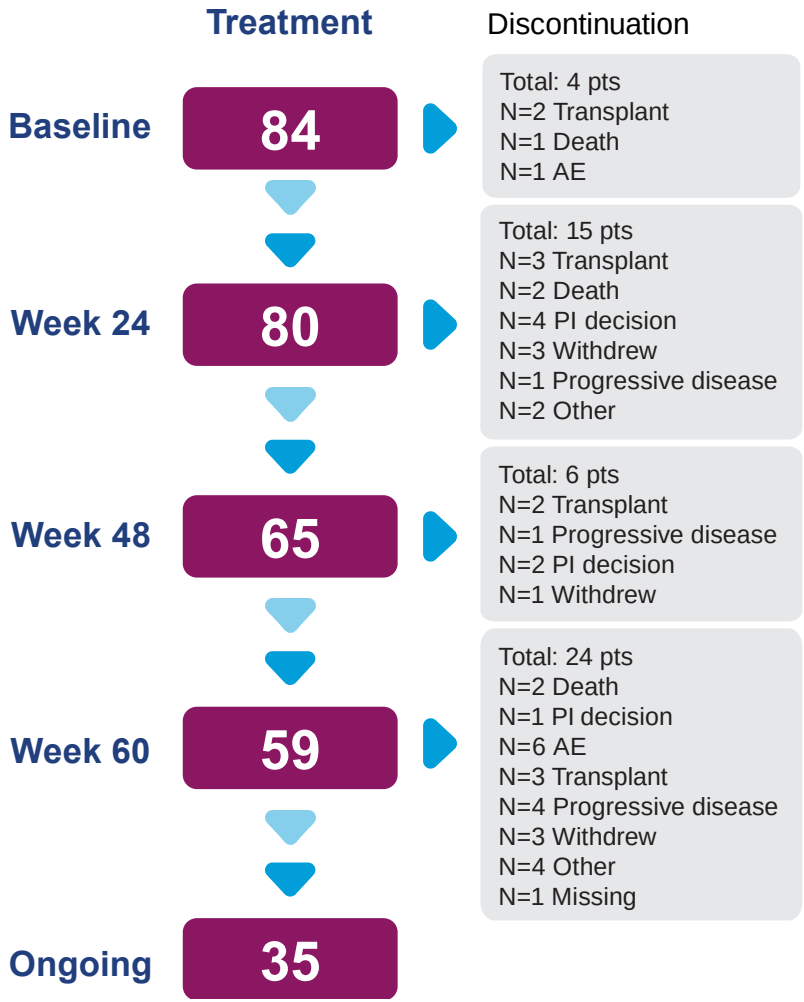
MANIFEST Arm 3: Patient disposition

	Arm 3
Enrolled (n)	84
Ongoing treatment [n (%)]	35 (42)
Discontinued treatment [n (%)]	49 (58)
Primary reason for treatment discontinuation [n (%)]	
Progressive disease	6 (7)
AE* or lab abnormality	7 (8)
Withdrew consent	7 (8)
PI decision	7 (8)
Death	5 (6)
Stem cell transplant	10 (12)
Other	6 (7)
Missing†	1 (1)
Pelabresib dose (median, range)	125 mg QD (50, 125)
Ruxolitinib dose (median, range)	10 mg BID (5, 25)

Median treatment duration‡: Median: 26.7 months (95% CI: 19.1–30.8)
46% (39/84) of patients were treated ≥2 years



*Two patients were initially discontinued due to AEs that later resulted in death.
†Pending data entry.
‡Kaplan-Meier estimate.
PD, progressive disease.

Data cutoff 29 July 2022

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MANIFEST Arm 3: Baseline demographics and disease characteristics

Characteristic		N=84
Age (years)	Mean (SD)	67 (10)
Gender	Male, n (%)	59 (70)
DIPSS	Int-1, n (%)	19 (23)
	Int-2, n (%)	52 (62)
	High, n (%)	13 (16)
IPSS	Int-1, n (%)	10 (12)
	Int-2, n (%)	29 (35)
	High, n (%)	45 (54)
MF subtype	Primary MF, n (%)	46 (55)
	Post-PV MF, n (%)	9 (11)
	Post-ET MF, n (%)	27 (32)
	Missing*, n (%)	2 (2)
Hemoglobin (g/dL)	Median (min, max)	9 (7, 17)
	<10, n (%)	55 (66)
Platelet (× 10^9/L)	Median (min, max)	294 (100, 1849)
Spleen volume (cc)	Median (min, max)	1698 (458, 4782)
TSS	Median (min, max)	16 (0, 38)
Mutations	HMR†, n (%)	47 (56)
	ASXL1, n (%)	37 (44)
	JAK2 V617F‡, n (%)	59 (70)
	CALR‡, n (%)	17 (20)
	MPL, n (%)	6 (7)
	Triple negative, n (%)	3 (4)

*Pending data entry; †HMR: High-molecular risk mutations: *ASXL1, EZH2, IDH1/2, SRSF2, U2AF1*; ‡One patient had both *JAK2 V617F* and *CALR* mutations.
ET, essential thrombocythemia; HMR, high-molecular risk; Int, intermediate; IPSS, International Prognostic Scoring System; PV, polycythemia vera.

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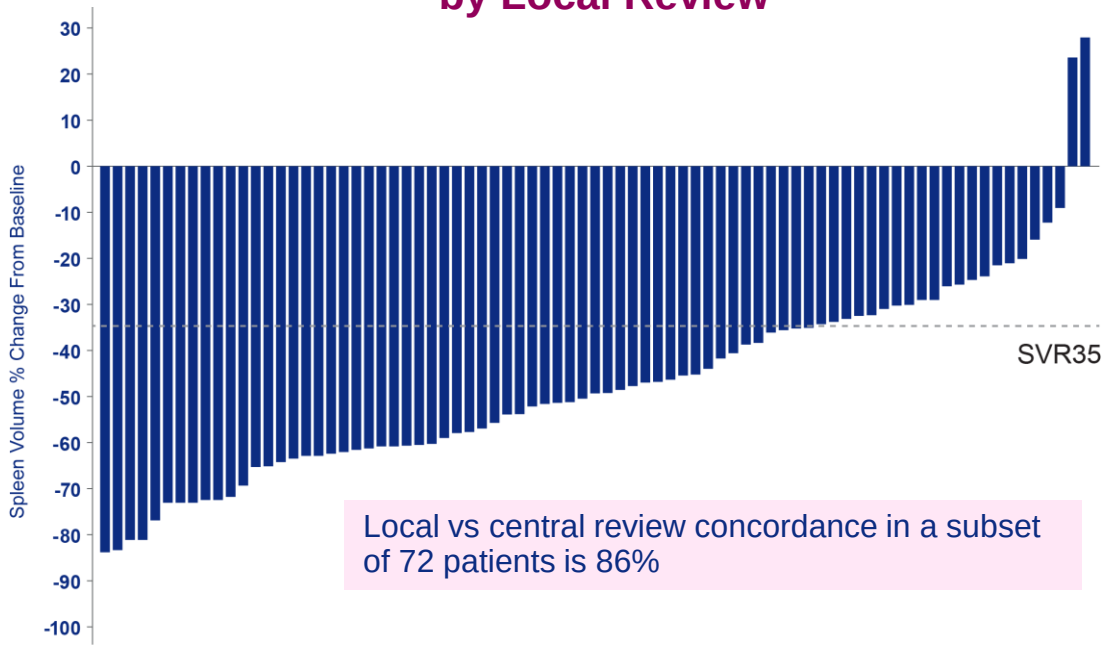
MANIFEST Arm 3: Spleen volume response at Week 24 and best reduction

Spleen Volume at Week 24, by Local Review



Local vs central review concordance in a subset of 72 patients is 86%

Best Reduction in Spleen Volume, by Local Review

	N=84
SVR35 at Wk 24	68% (57/84), 95% CI 57–78
Median % SVR	–50%
Mean % SVR	–48%
SVR35 at any time	80% (67/84), 95% CI 70–88

SVR: spleen volume reduction per local radiology review; central radiology review is ongoing.
Patients are evaluable for SVR35 at Wk 24 if they have had Wk 24 assessment by the data cutoff date or discontinued without Wk 24 assessment at any time.

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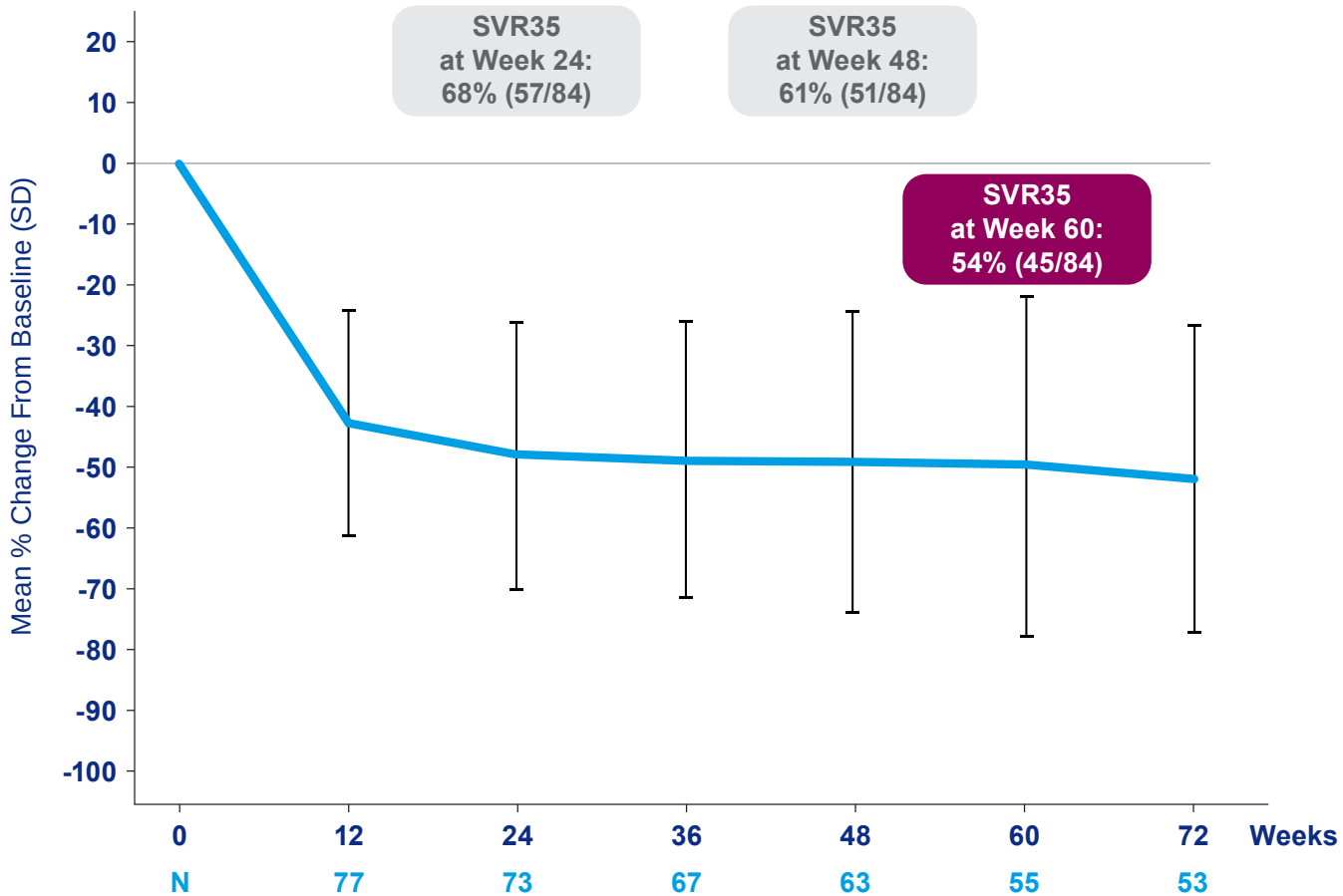
MANIFEST Arm 3: Spleen volume response over time

Spleen Volume Mean Percentage Change Over Time



N=84	
Median time to SVR35 response	12 wks (range 10–51)
Median follow-up* for SVR35 response	84 wks (95% CI 66–90)
Response maintained at data cutoff	70% (47/67)

*Median has not been reached; reverse Kaplan–Meier estimate of median duration of follow-up for SVR35 response.
Spleen volume per local radiology review. Spleen volume mean percentage change: patients with available spleen volume assessment for the corresponding time points.

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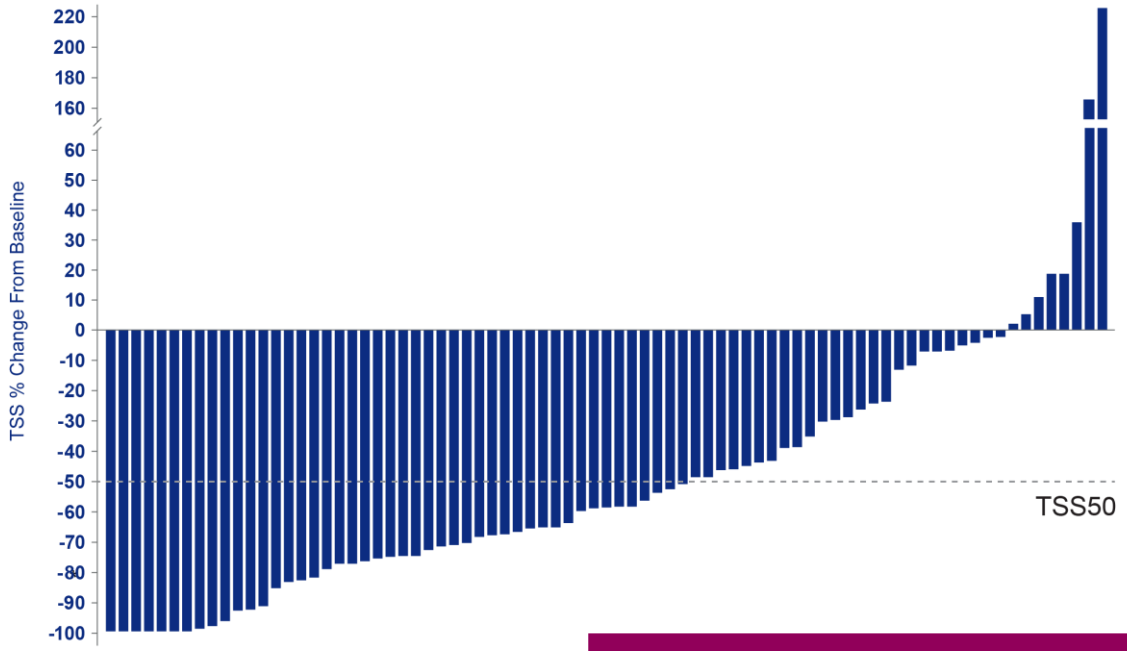
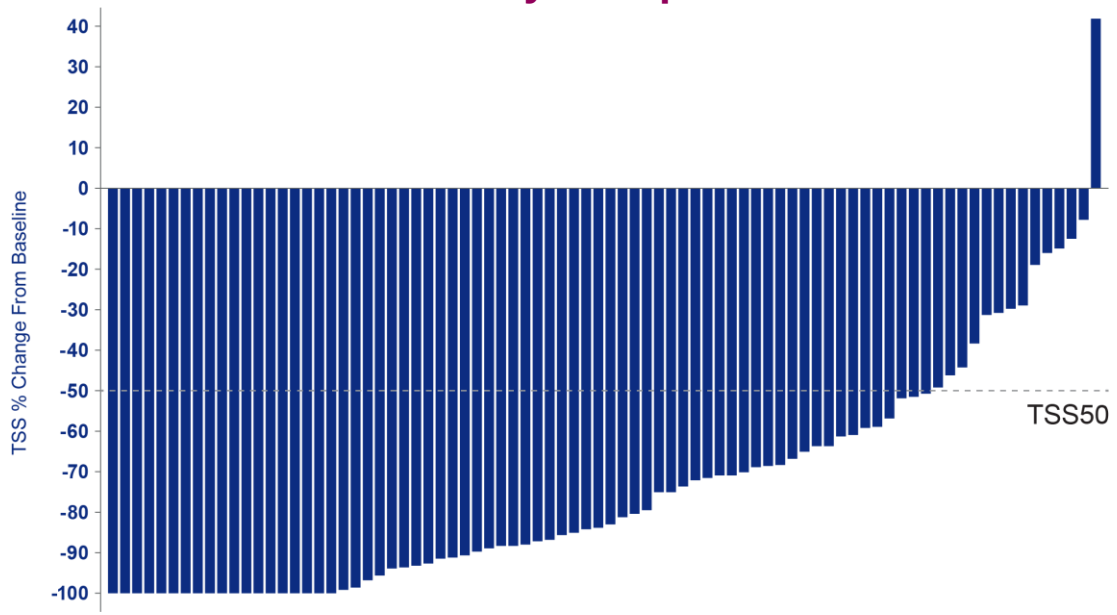
MANIFEST Arm 3: Change in total symptom score at Week 24 and best reduction at any timepoint

Change in Total Symptom Score at Week 24



Total Symptom Score: Best Reduction at Any Timepoint



	N=84
TSS50 at Week 24	56% (46/82*), 95% CI 45–67
Median TSS % change	–59%
Mean TSS % change	–47%
TSS50 at any time	83% (68/82*), 95% CI 73–90

*Two ongoing patients were nonevaluable for TSS50; n=1 due to missing baseline, n=1 due to baseline TSS=0.
Patients are evaluable for TSS50 at Wk 24 if they have had Wk 24 TSS assessment by the data cutoff date or discontinued without Wk 24 assessment at any time.

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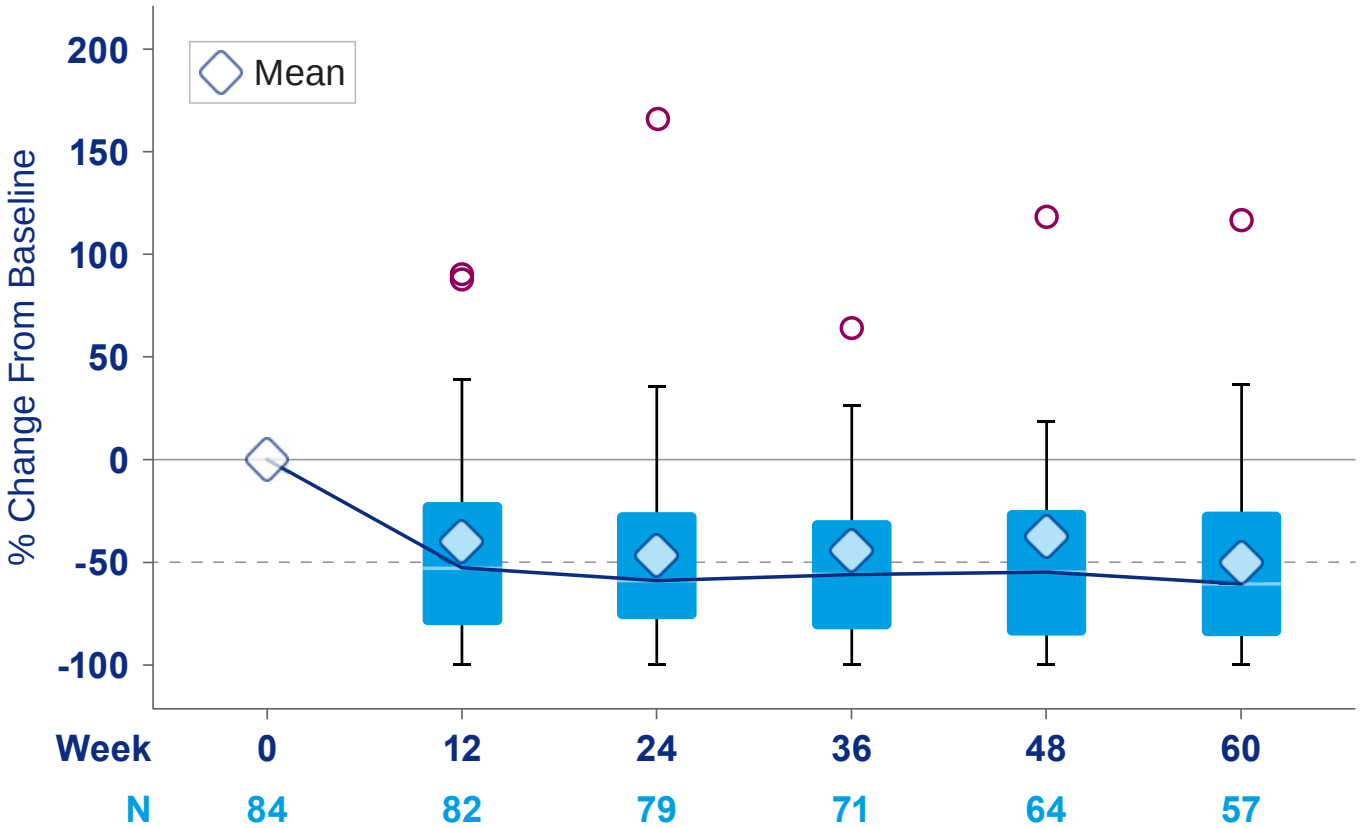
MANIFEST Arm 3: Change in total symptom score over time

TSS Mean Percentage Change Over Time



	TSS50
Week 24	56% (46/82)
Week 48	44% (36/82)
Week 60	43% (35/82)

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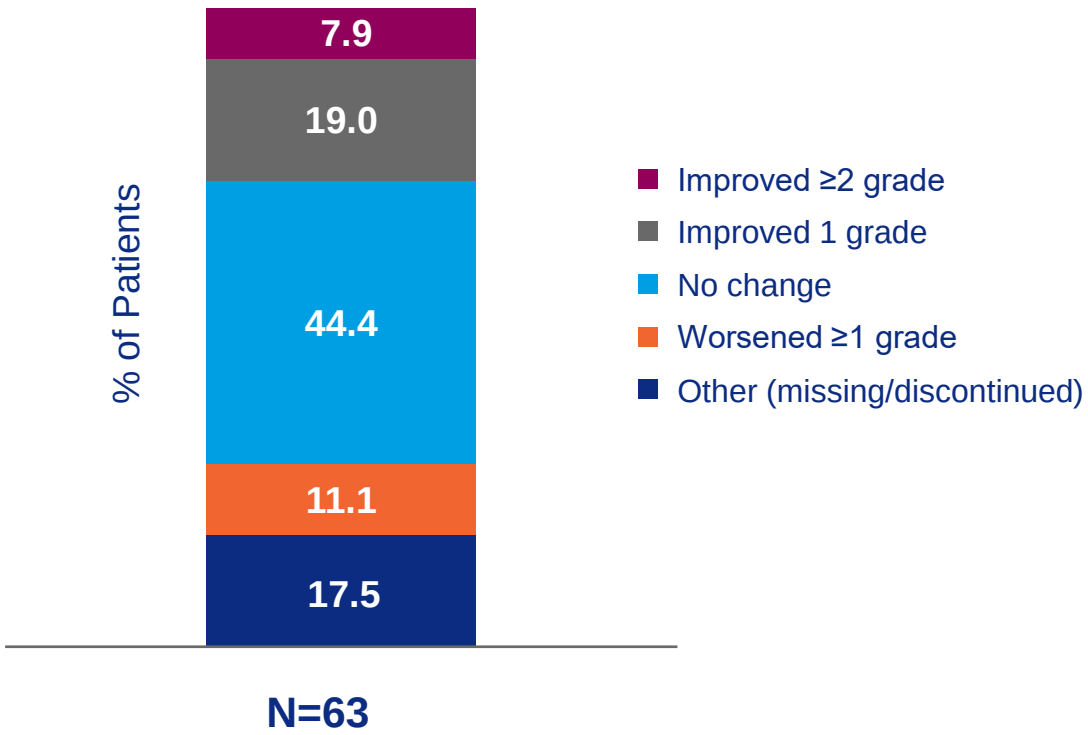
MANIFEST Arm 3: Change in bone marrow fibrosis grade at Week 24

Change in Bone Marrow Fibrosis Grade at Week 24 by Central Pathology Review



- 27% (17/63) of patients showed ≥1 grade improvement at Week 24
  - This improvement was maintained in 59% (10/17) of patients at the next available assessment or longer
- 40% (25/63) of patients had ≥1 grade improvement at any time

Patients evaluable if nonmissing baseline or discontinued without Week 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.

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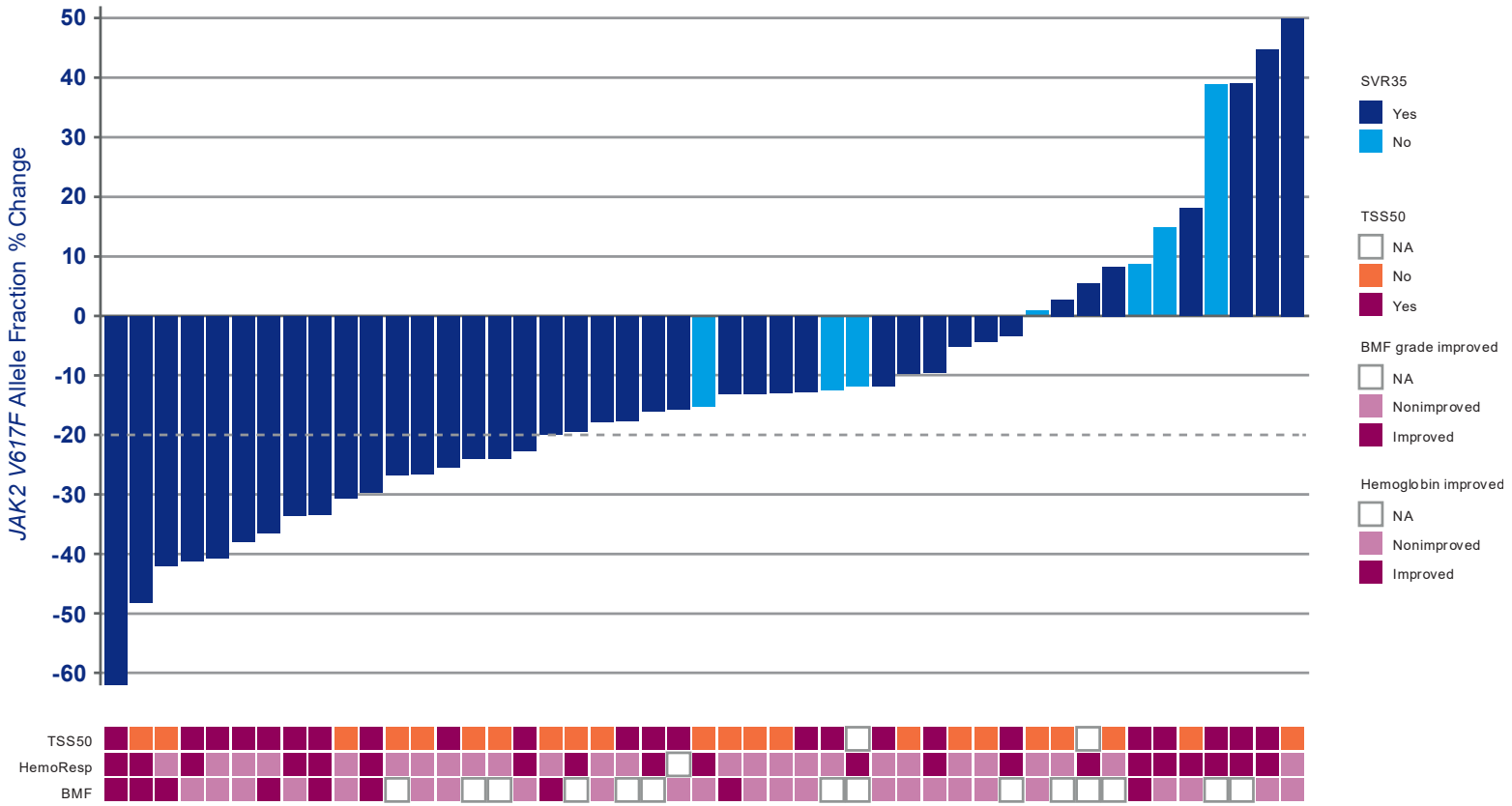
MANIFEST Arm 3: Overlapping clinical responses associated with *JAK2 V617F* VAF reduction at Week 24



- 18/47 (38%) patients reached ≥20% reduction in *JAK2 V617F* VAF
  - Median (min, max) reduction was –14% (–62%, 50%)

Hgb assessment within 2 weeks after RBC transfusion were excluded from the analysis; any level of increase from baseline (range: 0.1–3.8 g/dL).

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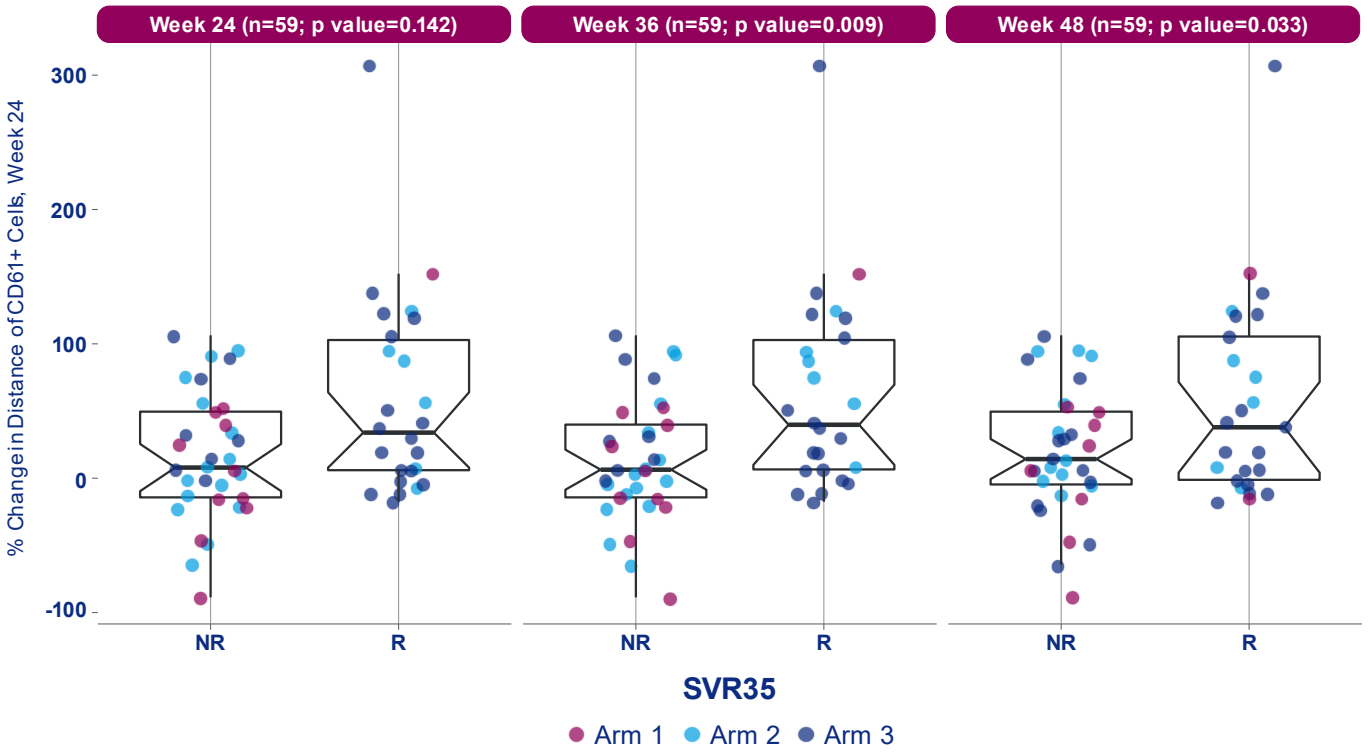
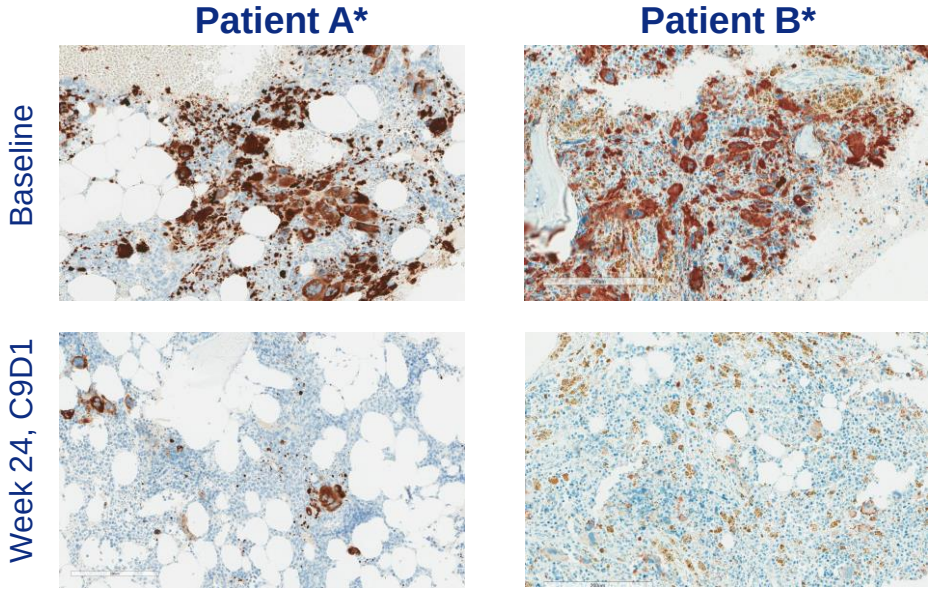
Correlation between megakaryocyte ‘declustering’ in bone marrow and SVR35 response



SVR35 responders



Slide pairs were stained centrally for CD61; scanned and digital images were evaluated for CD61 distance.
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.

Clinical Benefit Associated With Biomarker Changes Indicative of Disease Modification in Patients With Myelofibrosis Treated With the BET Inhibitor Pelabresib as Monotherapy or in Combination With Ruxolitinib
Scandura J, et al. Oral presentation 630, Dec 11, 5:45 pm EST

*Images and examination results used with patient consent. Data previously presented at EHA 2022 Annual Meeting, June 9–12, 2022; Vienna, Austria.
P values were computed by logistic regression with age and gender adjustment.
CD61, platelet glycoprotein IIIa; NR, nonresponders; R, responders.

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MANIFEST Arm 3: Summary of adverse events

TEAEs of all grades that occurred in ≥20% of patients		All Grade N=84* n (%)	Grade 3 N=84* n (%)	Grade 4 N=84* n (%)
Hematologic Events	Anemia	36 (43%)	28 (33%)	1 (1%)
	Thrombocytopenia†	46 (55%)	12 (14%)	3 (4%)
Nonhematologic Events	**Gastrointestinal events**			
	Diarrhea	36 (43%)	2 (2%)	0
	Constipation	25 (30%)	0	0
	Nausea	24 (29%)	0	0
	Abdominal pain‡	22 (26%)	0	0
	Other nonhematologic events			
	Respiratory tract infection§	34 (41%)	8 (10%)	2 (2%)
	Asthenic conditions¶	32 (38%)	1 (1%)	1 (1%)
	Musculoskeletal pain**	27 (32%)	0	0
	Dizziness††	23 (27%)	0	0
	Cough	20 (24%)	0	0
	Dysgeusia	20 (24%)	0	0
	Dyspnea	19 (23%)	4 (5%)	0
	Headache	18 (21%)	0	0
	Muscle spasms	17 (20%)	0	0

- Serious adverse events reported in ≥2 pts were anemia, pyrexia and COVID-19 (3 pts each), gastrointestinal hemorrhage, multiple organ dysfunction syndrome, COVID-19 pneumonia, pneumonia, respiratory tract infection, urinary tract infection, fall and respiratory failure (two pts each)
- Twelve pts (14%) reported TEAEs that led to pelabresib discontinuation
- Eight Gr 5 TEAEs were reported in 7 pts
  - Acute respiratory distress syndrome due to ruxolitinib withdrawal (2 pts each), multiorgan failure (MOF) due to COVID (reported as two separate TEAEs in the same pt), MOF due to sepsis secondary to pneumonia, respiratory failure due to COVID-19, bacterial endocarditis and urinary tract infection
  - 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 upper respiratory tract infection, viral upper respiratory tract infection, bronchitis, sinusitis, rhinitis, nasopharyngitis, pneumonia, COVID-19, COVID-19 pneumonia and influenza; ¶Include TEAEs of asthenia, fatigue, lethargy and malaise; **Includes TEAEs of arthralgia and myalgia; ††Includes TEAEs of balance disorder and vertigo.

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MANIFEST Arm 3: Conclusions

- The combination of pelabresib and ruxolitinib in JAKi-naïve patients with myelofibrosis showed durable improvements in spleen volume, total symptom score and bone marrow fibrosis; safety data were consistent with previous results
- Clinical data showed durable responses beyond Week 24
  - SVR35: 68% at Week 24, 54% at Week 60, 80% at any time
  - TSS50: 56% at Week 24, 43% at Week 60, 83% at any time
- ≥1 grade improvement in bone marrow fibrosis at Week 24 was reported in 27% of patients, and 40% had an improvement of one grade or higher at any time
- 'Declustering' of megakaryocytes in the bone marrow and reductions in *JAK2 V617F* VAF correlated with SVR35 responses
- No new safety signals were observed with a longer follow-up of 11 additional months. The most common treatment-emergent adverse events were low grade
- MANIFEST-2, a Phase 3 randomized double-blind trial of pelabresib + ruxolitinib vs placebo + ruxolitinib in JAKi treatment-naïve patients with myelofibrosis, has been initiated and is open for enrollment (NCT04603495)[1]

1. Clinicaltrials.gov. NCT04603495. Available at: https://clinicaltrials.gov/ct2/show/NCT04603495. Accessed November 10, 2022.

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