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

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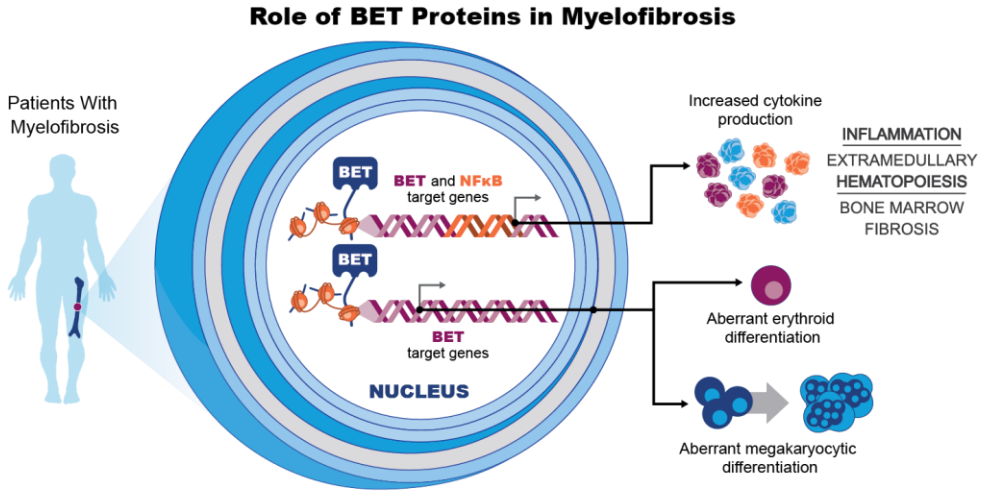
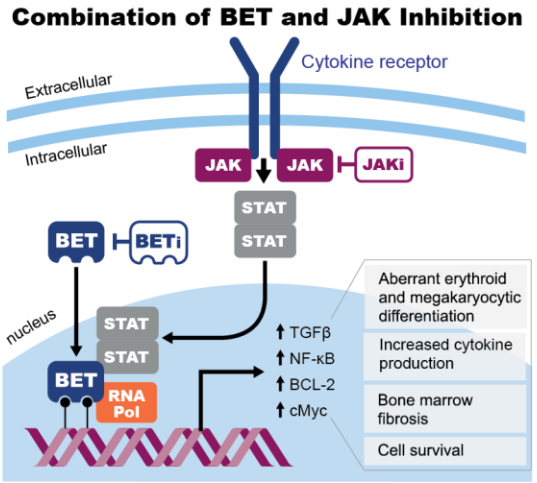
Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

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[1]
- Unmet medical need persists due to limited efficacy with currently available JAKi monotherapy, high rates of discontinuation and toxicities[1]
- Preclinical data indicated non-overlapping activity 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; JAKi, Janus kinase inhibitor; 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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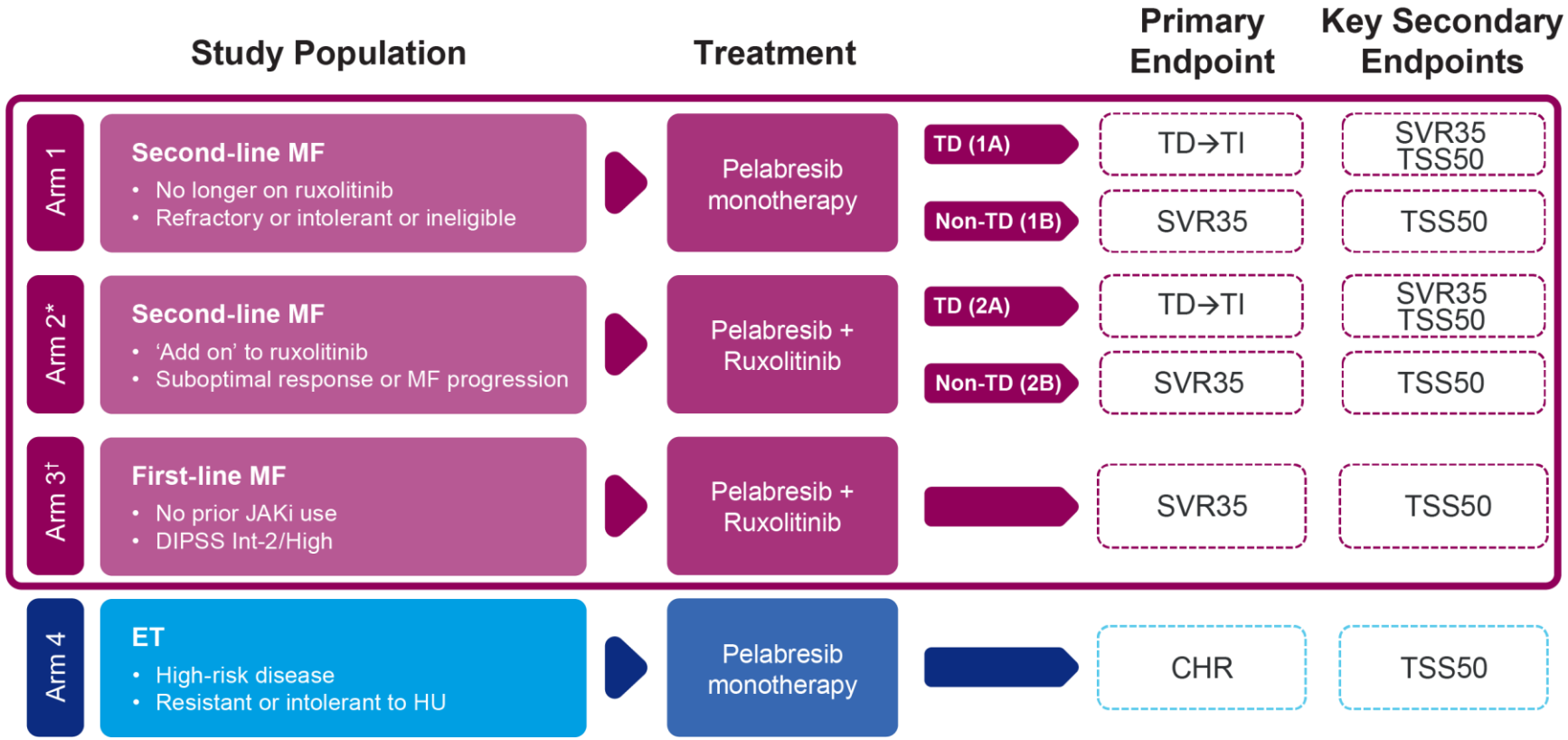
MANIFEST: Ongoing, global, open-label Phase 2 study investigating pelabresib in myelofibrosis and essential thrombocythemia



**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

†*Pelabresib (CPI-0610) Combined With Ruxolitinib for JAK Inhibitor Treatment-Naïve Patients With Myelofibrosis: Durability of Response and Safety Beyond Week 24* — Mascarenhas J, et al. Oral presentation 238, Dec 10, 2:45 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; 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.

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

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Multivariable biomarker analysis

A comprehensive exploratory analysis of pelabresib +/- ruxolitinib treatment effects

- Association of clinical outcomes/endpoints:
  - Spleen volume changes (SVR35)
  - Symptom improvement (TSS50)
  - Anemia improvement/hemoglobin increase
- With changes in biomarkers:
  - *JAK2 V617F* VAF
  - BM morphology (fibrosis, megakaryocyte morphology)
  - Plasma cytokines

VAF, variant allele fraction.

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MANIFEST: Clinical responses and changes in biomarkers at Week 24

Parameters assessed at Week 24		Arm 1	Arm 2	Arm 3	Overall
		• Pelabresib monotherapy • Ruxolitinib intolerant, ineligible or refractory patients with MF	• Pelabresib 'add-on' to ruxolitinib • Patients with MF with suboptimal response to ruxolitinib	• Pelabresib + ruxolitinib • JAKi-naïve patients with MF	
Clinical responses	**SVR35**	10/88 (11%)	15/86 (17%)	57/84 (68%)	82/258 (32%)
	TSS50	22/88 (25%)	32/85 (38%)	46/82 (56%)	100/255 (39%)
	Increase* in Hgb levels	31/96 (32%)	24/87 (28%)	29/84 (35%)	84/267 (32%)
Biomarkers indicative of disease modification	**Improvements in BM fibrosis of ≥1 grade**	10/60 (17%)	13/51 (26%)	17/63 (27%)	40/174 (23%)
	≥15% increase in distance between nuclei of CD61+ cells in BM [median change]	5/11 (46%) [+5.8%]	9/21 (43%) [+8.4%]	16/27 (59%) [+28.4%]	30/59 (51%)
	≥20% reduction in *JAK2 V617F* VAF (≥20% reduction in allelic fraction)	2/35 (6%)	4/31 (13%)	18/47 (38%)	24/113 (21%)

*Hgb assessment within 2 weeks after RBC transfusion were excluded from the analysis; any level of increase from baseline (ranges of increase: Arm 1, 0.1–4.2 g/dL; Arm 2, 0.1–2.5 g/dL; Arm 3, 0.1–3.8 g/dL).

Data cutoff 29 July 2022

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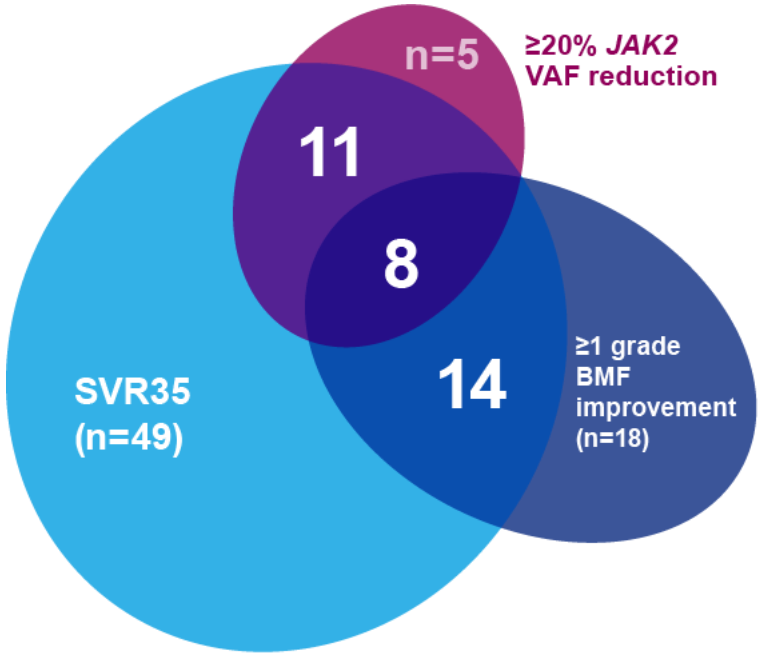
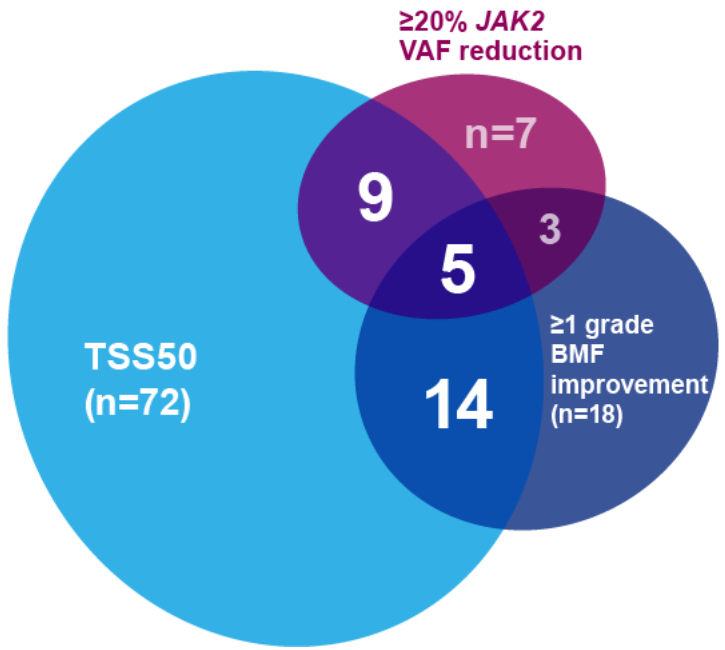
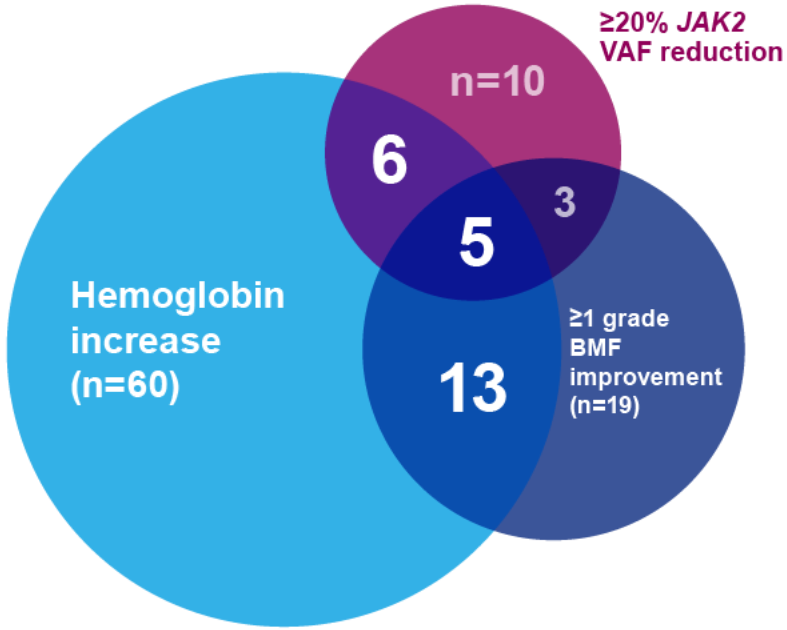
MANIFEST Arms 1–3: Clinical responses associated with *JAK2 V617F* VAF reduction and ≥1 grade improvement in BMF at Week 24



33/82 (40%) of SVR35 responders had *JAK2 V617F* VAF reduction and/or BMF improvement



28/100 (28%) of TSS50 responders had *JAK2 V617F* VAF reduction and/or BMF improvement



24/84 (29%) patients with hemoglobin improvement had *JAK2 V617F* VAF reduction and/or BMF improvement

All patients who had clinical responses, *JAK2 V617F* VAF reduction and BMF improvement at Week 24 were JAKi treatment naïve (Arm 3)

Hemoglobin increase: Hgb assessment within 2 weeks after RBC transfusion were excluded from the analysis; any level of increase from baseline (ranges of increase: Arm 1, 0.1–4.2 g/dL; Arm 2, 0.1–2.5 g/dL; Arm 3, 0.1–3.8 g/dL).

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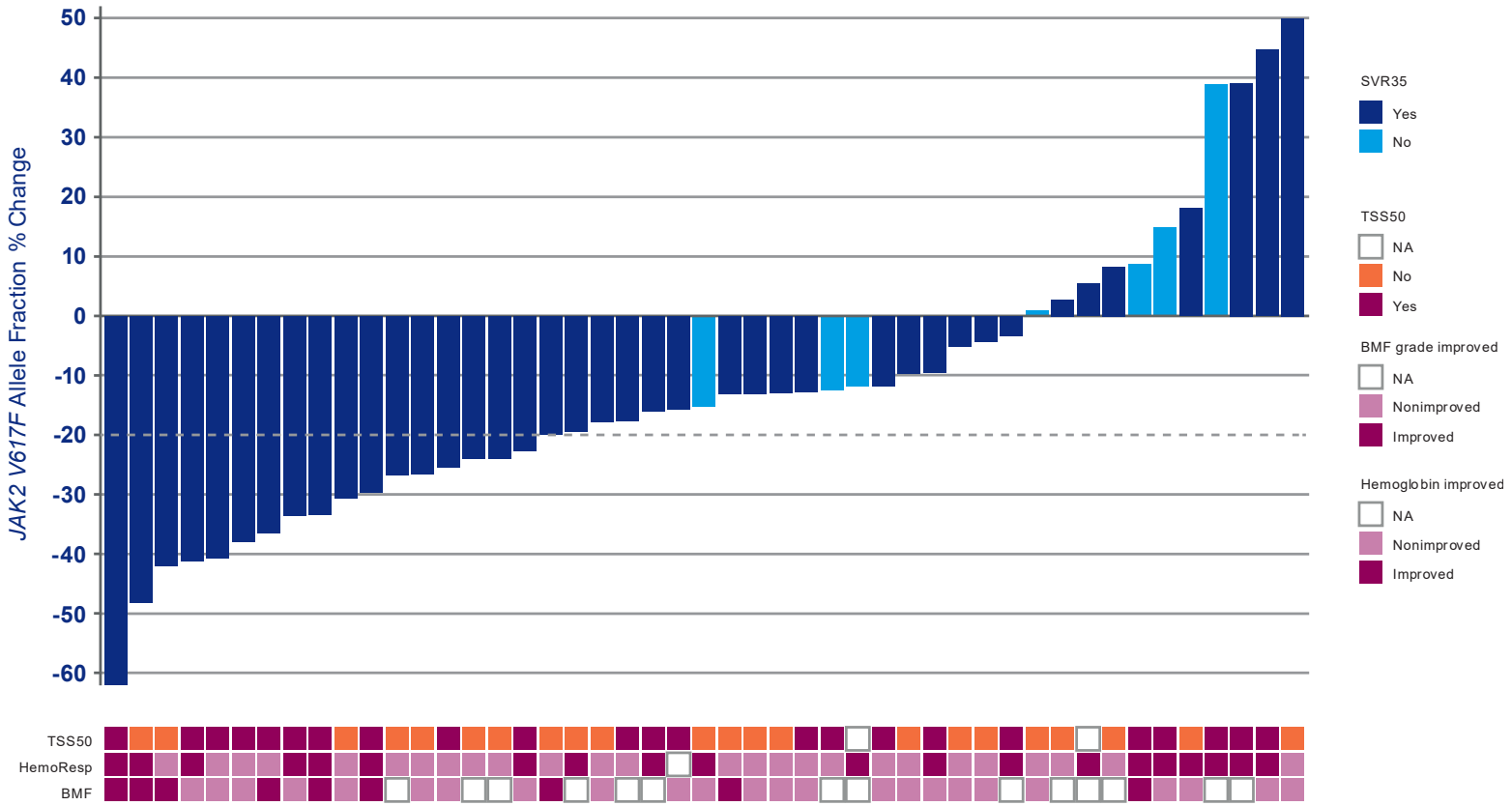
MANIFEST Arm 3: Overlapping clinical responses associated with *JAK2 V617F* VAF reduction at Week 24



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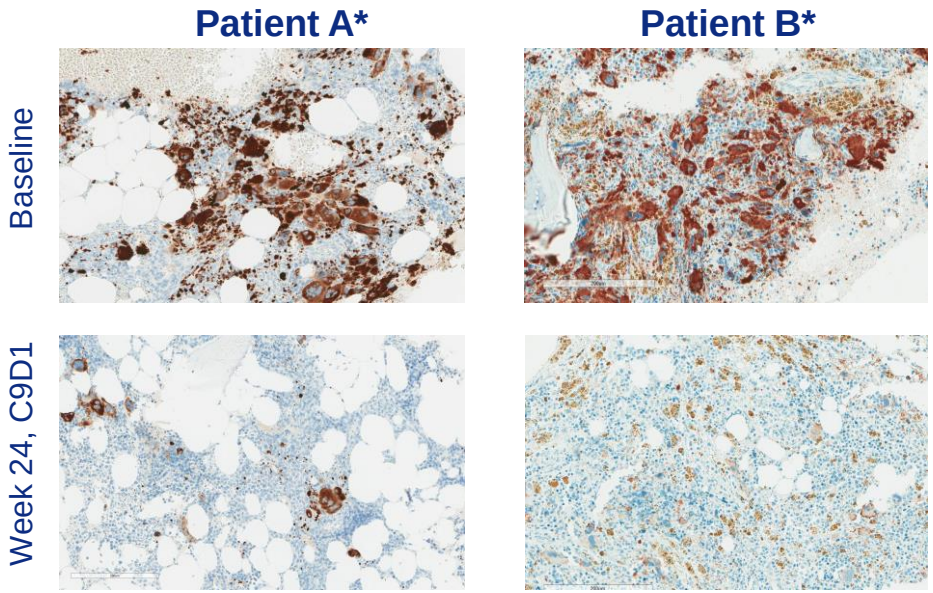
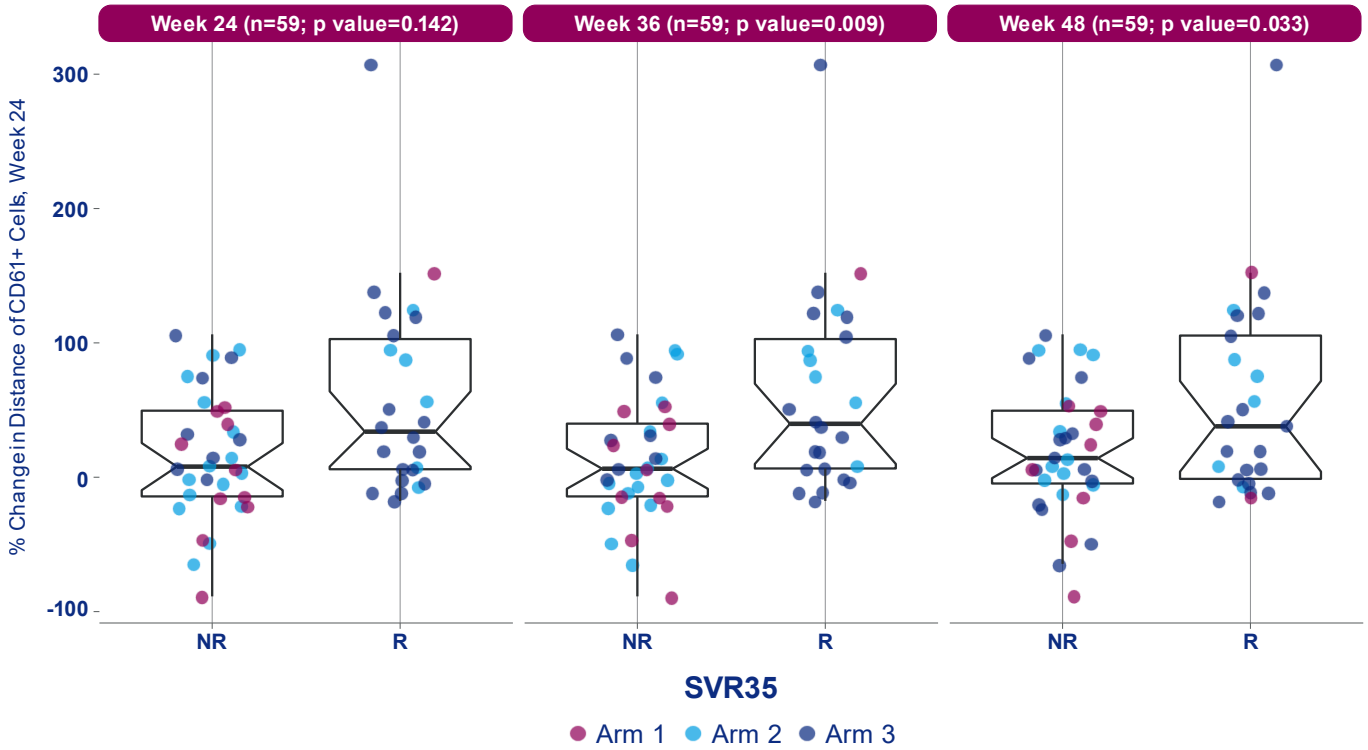
Correlation between megakaryocyte ‘declustering’ in bone marrow and SVR35 response

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.



*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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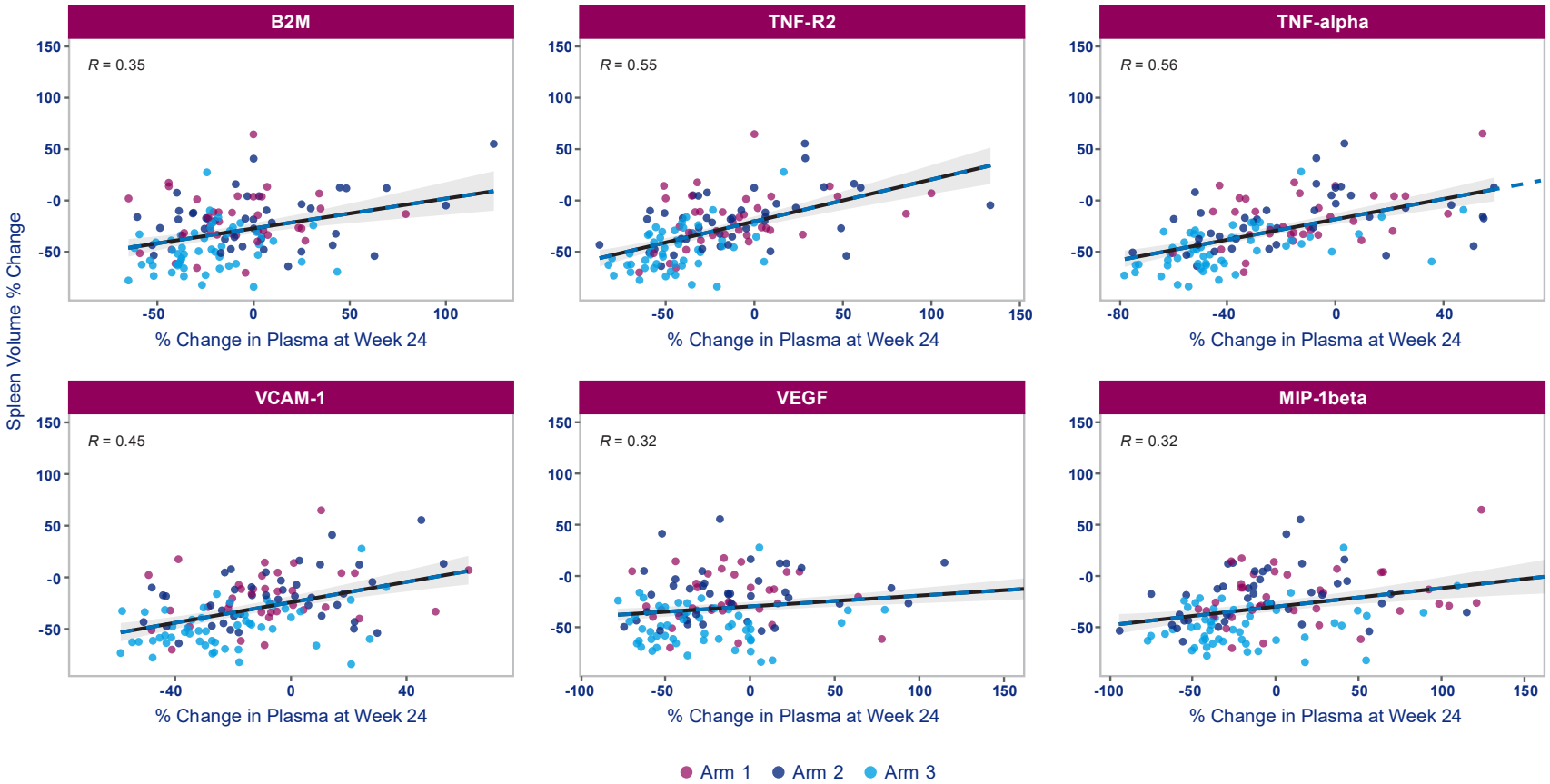
Correlation of plasma cytokine changes with spleen volume changes at Week 24



Overview of Cytokines

Cytokine	NF-kB signaling	MF elevated
B2M	√	
TNF-R2	√	√
TNF-alpha	√	√
VCAM-1	√	√
VEGFa	√	√
MIP-1beta	√	√

- Reduction in plasma levels of cytokines was associated with spleen volume reduction at Week 24

NF-κB, nuclear factor kappa B.

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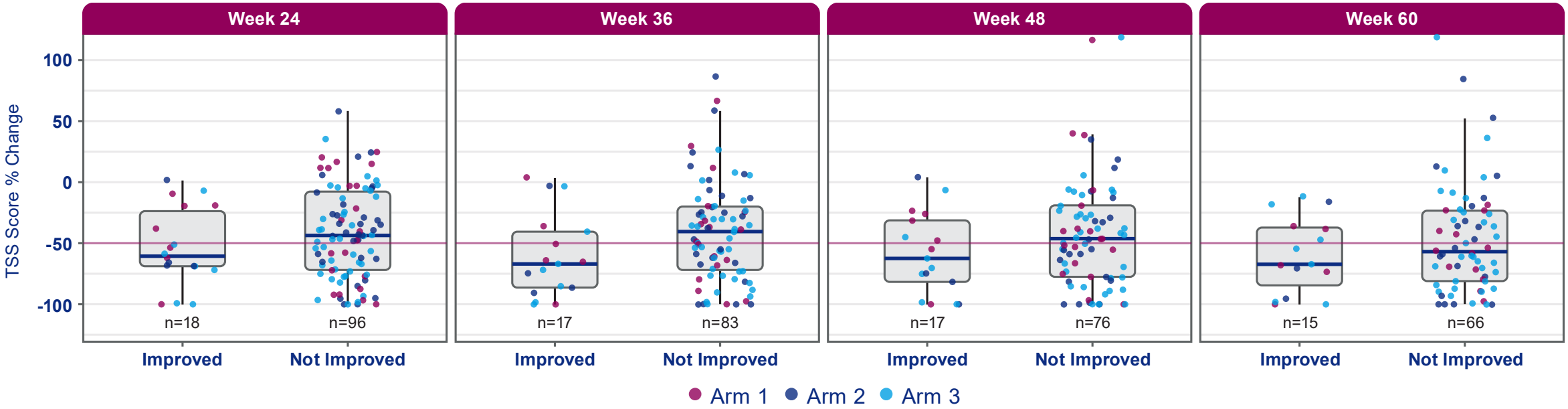
Hemoglobin and bone marrow fibrosis improvements at Week 24 correlates with TSS responses



Patients with hemoglobin increase* AND ≥1 grade BMF improvement at Week 24 respond with a more profound TSS score change

*Hgb assessment within 2 weeks after RBC transfusion were excluded from the analysis; any level of increase from baseline (ranges of increase: Arm 1, 0.1–4.2 g/dL; Arm 2, 0.1–2.5 g/dL; Arm 3, 0.1–3.8 g/dL).

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Conclusions

- Exploratory biomarker analysis of the MANIFEST trial showed an association of BMF and VAF reductions with SVR35, TSS50 and hemoglobin responses in treatment-naïve patients
- Hemoglobin and bone marrow fibrosis improvements correlated with symptom reduction at Week 24
- Decrease of proinflammatory plasma cytokines at Week 24 was significantly associated with spleen volume reduction
- Collectively, these biomarker data suggest potential biological response modification
- 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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Acknowledgements

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