

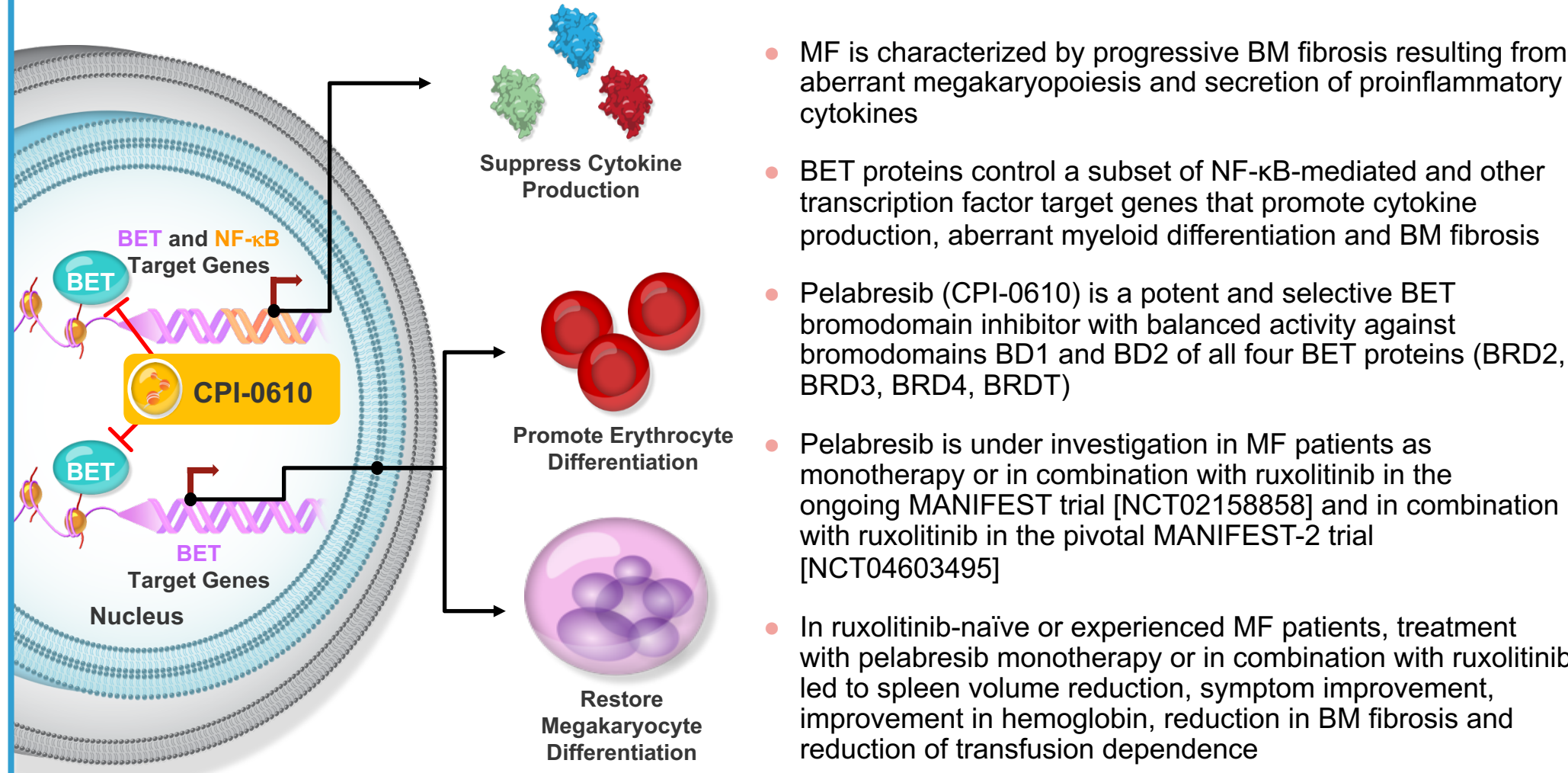
BET Inhibitor Pelabresib (CPI-0610) Decreases Inflammatory Cytokines, Improves Bone Marrow Fibrosis and Function, and Demonstrates Clinical Response Irrespective of Mutation Status in Myelofibrosis Patients in the Phase 2 MANIFEST Trial

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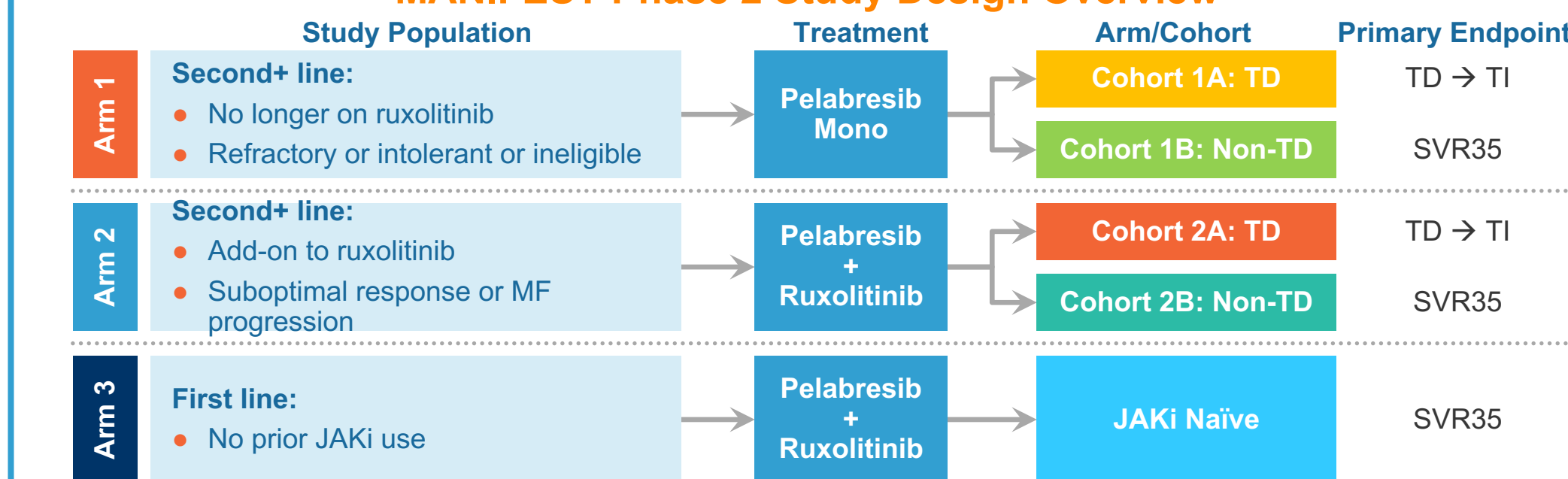
Background

BET Inhibitor Pelabresib in MF



Methods

MANIFEST Phase 2 Study Design Overview

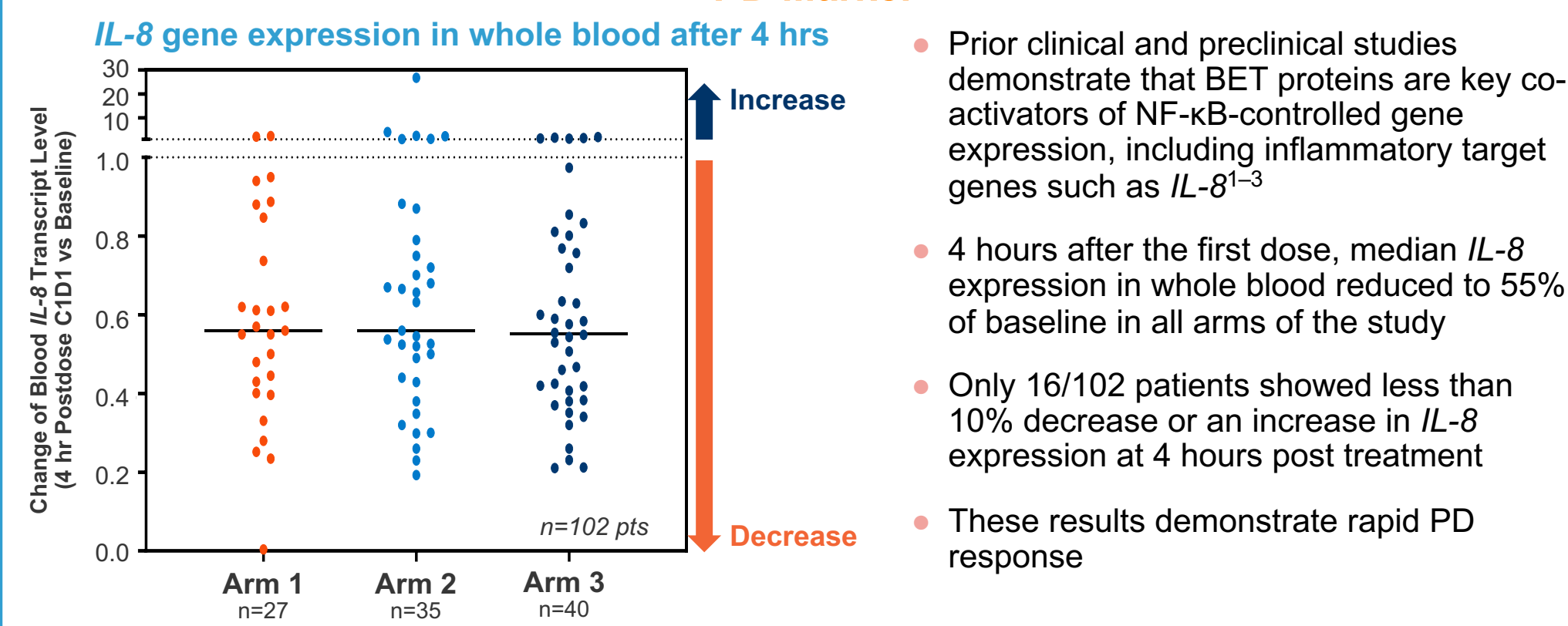


Assessment of Cytokines, Bone Marrow Fibrosis and Mutation Status in MANIFEST Patients

Translational Endpoint	Method
<i>IL-8</i> (<i>CXCL8</i>) gene expression	Peripheral blood qRT-PCR predose and 4 hours post dose on C1D1
Plasma cytokine levels	ELISA analysis of plasma cytokine levels at baseline compared with healthy donors, and response of cytokines to treatment at 14 days and longitudinally at 6, 12 and 24 weeks post treatment
BM fibrosis grade	Central review analysis of reticulin fibrosis staining on BM biopsy at baseline and 24+ weeks post treatment
Bone marrow erythroid progenitors and megakaryocytes	Exploratory IHC analysis of erythroid progenitors and megakaryocyte numbers, and clustering by staining for CD71 (erythrocyte progenitors) and CD61 (megakaryocyte) at baseline and 24 weeks
Ex vivo erythroid differentiation	Ex vivo differentiation of CD34+ cells from baseline patient samples with erythroid differentiation-promoting cytokines
Mutation profiling	Peripheral blood next-generation sequencing panel at baseline to identify mutations and correlate with response

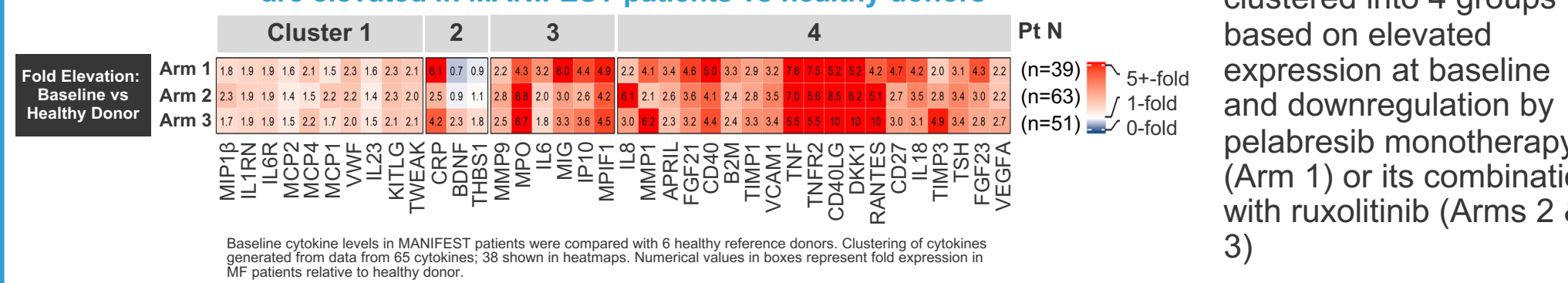
BET, bromodomain and extraterminal; BM, bone marrow; C1D1, Cycle 1 Day 1; CFU-E, erythroid progenitor cell; DMSO, dimethylsulfoxide; IHC, immunohistochemistry; IL-8, interleukin-8; IL-18, interleukin-18; JAKi, janus kinase inhibitor; MF, myelofibrosis; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B; Non-TD, nontransfusion-dependent; PD, pharmacodynamic; qRT-PCR, quantitative real-time polymerase chain reaction; SVR35, spleen volume reduction of at least 35%; TD, transfusion-dependent; TI, transfusion independent; TNFα, tumor necrosis factor α.

Rapid Reduction of *IL-8* (*CXCL8*) Gene Expression in Patient Blood as a PD Marker

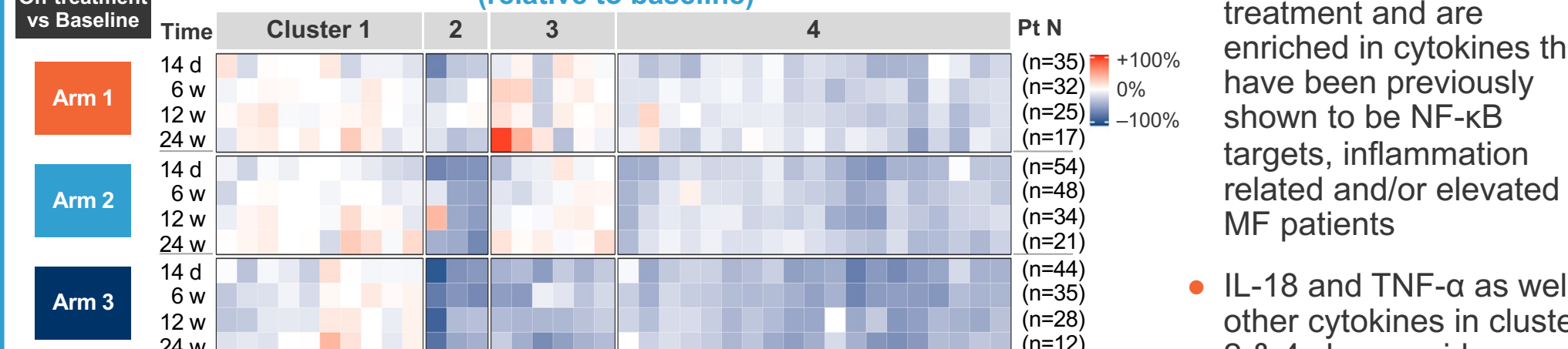


Pelabresib and Combination With Ruxolitinib Decrease Levels of NF-κB- and Inflammation-Related Cytokines in MANIFEST Patients

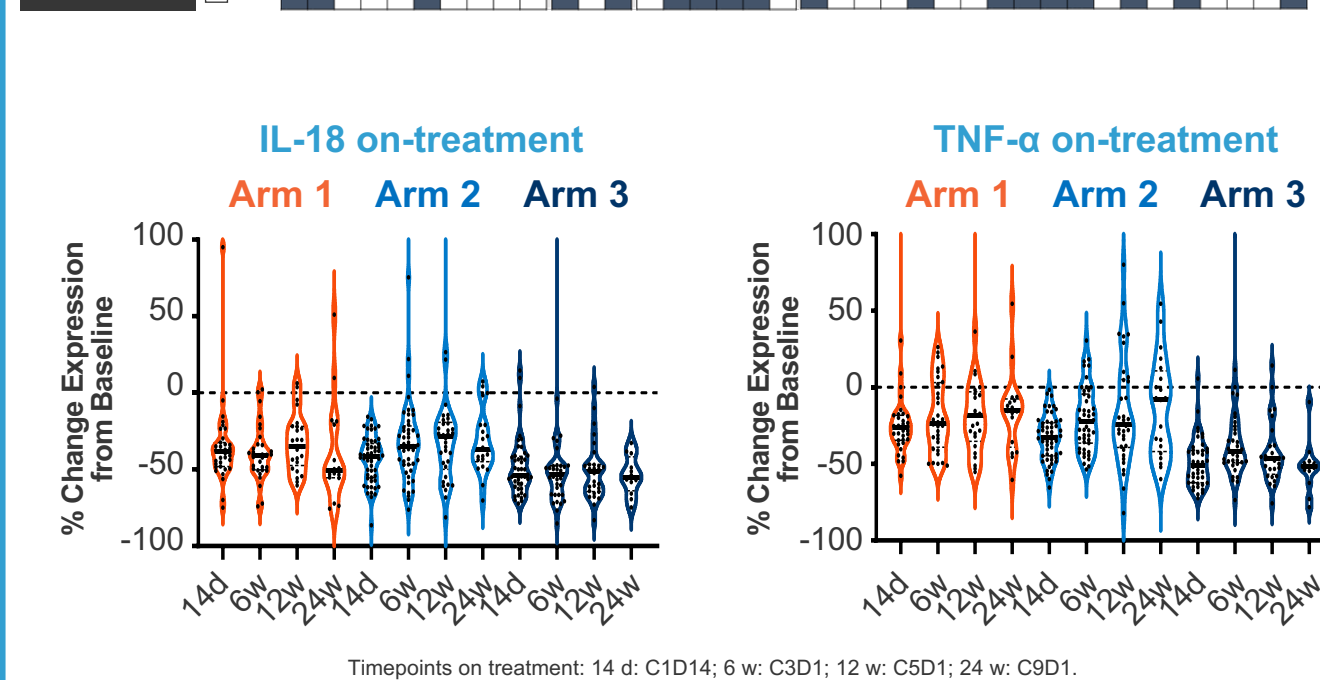
Baseline NF-κB- and inflammation-related cytokine levels are elevated in MANIFEST patients vs healthy donors



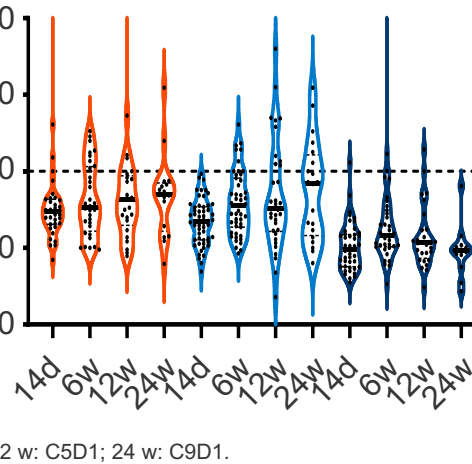
Decrease in cytokine levels after treatment with pelabresib and combination with ruxolitinib (relative to baseline)



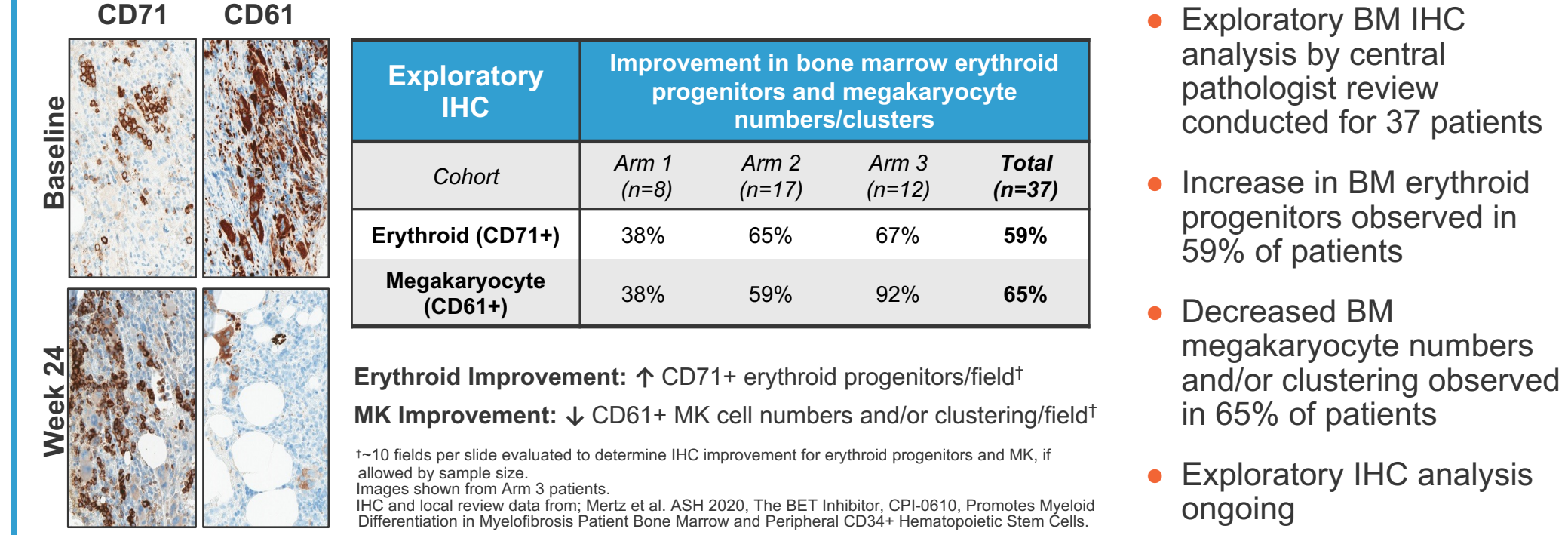
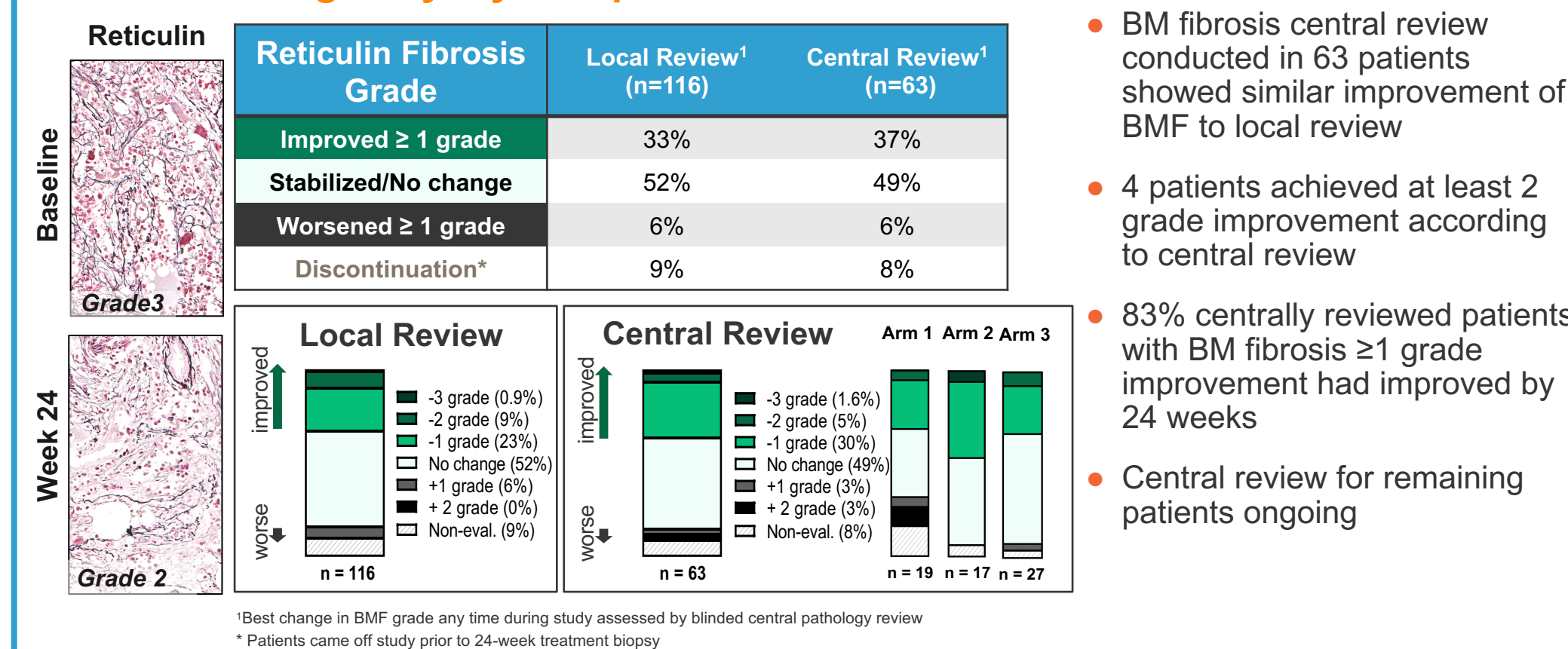
IL-18 on-treatment



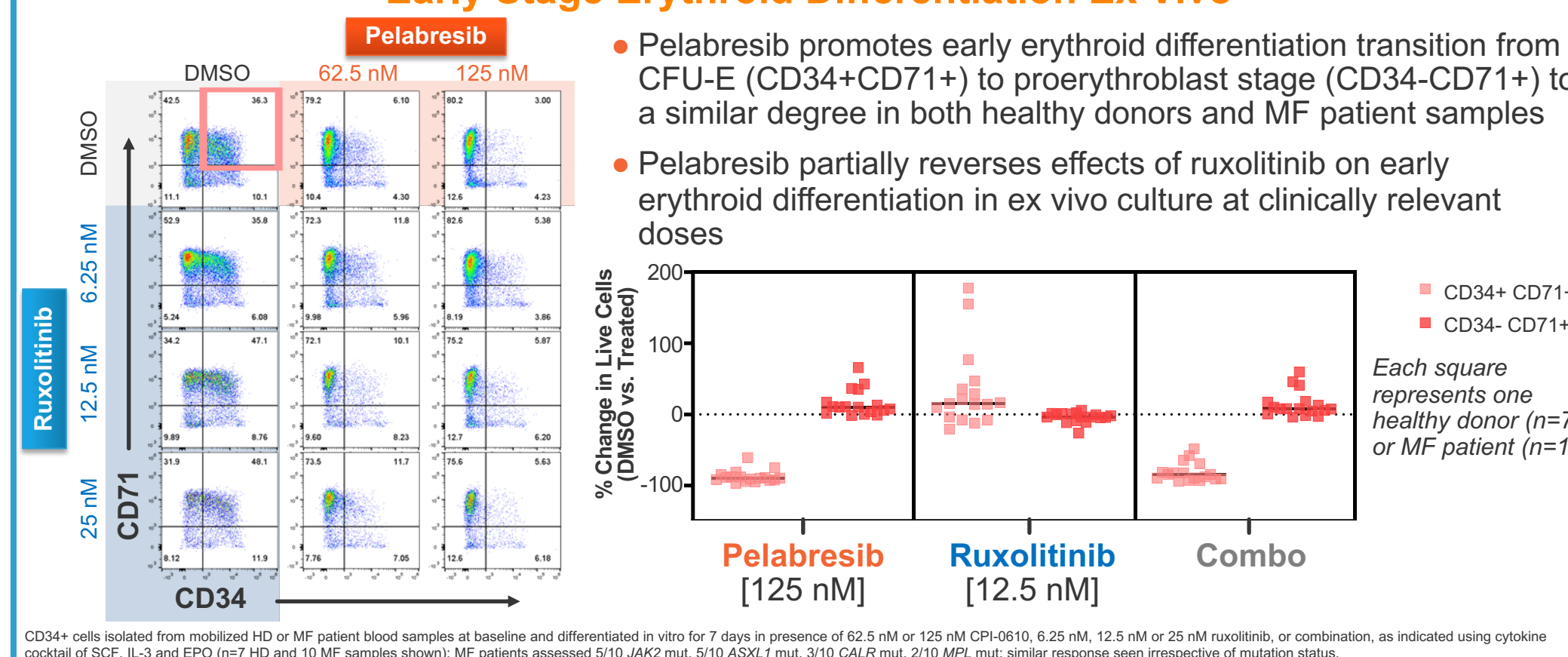
TNF-α on-treatment



MANIFEST Patients Show Improvements in BM Fibrosis and Erythroid and Megakaryocyte Populations After 24+ Weeks of Treatment



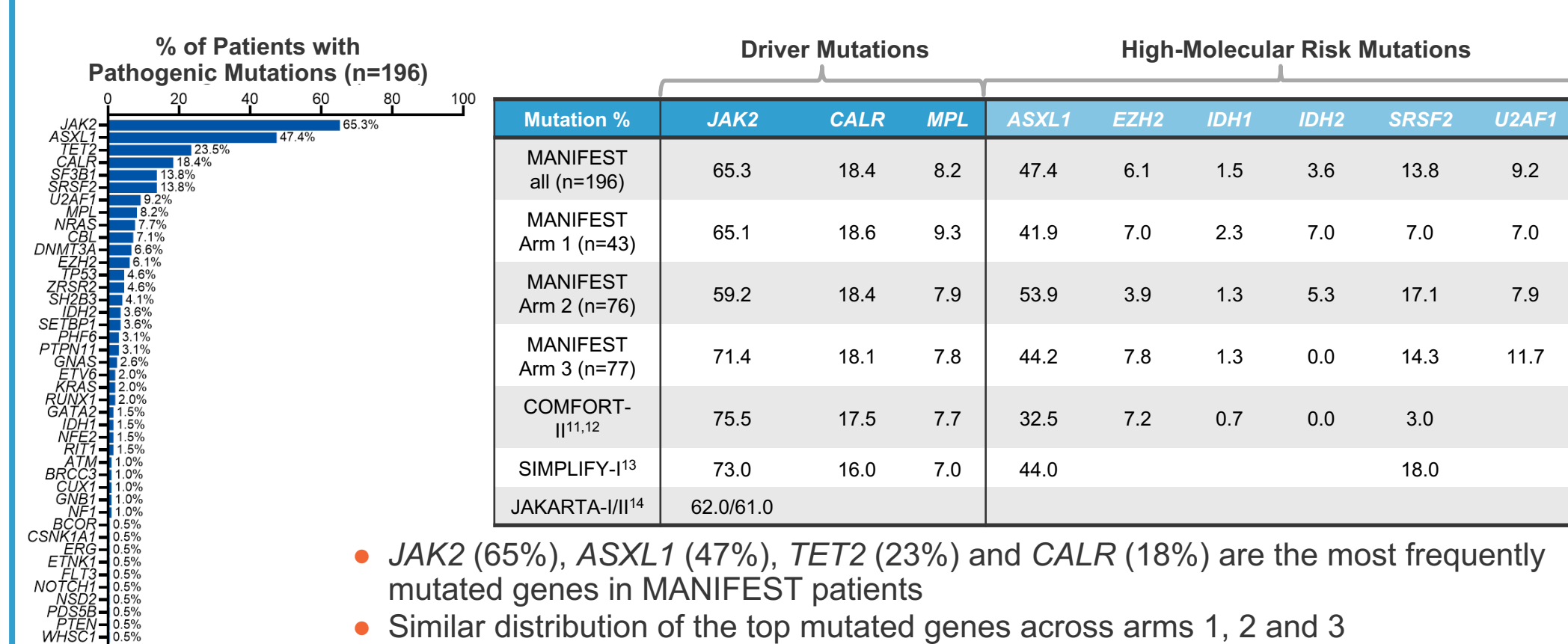
Pelabresib Partially Reverses Ruxolitinib-Mediated Suppression of Early Stage Erythroid Differentiation Ex Vivo



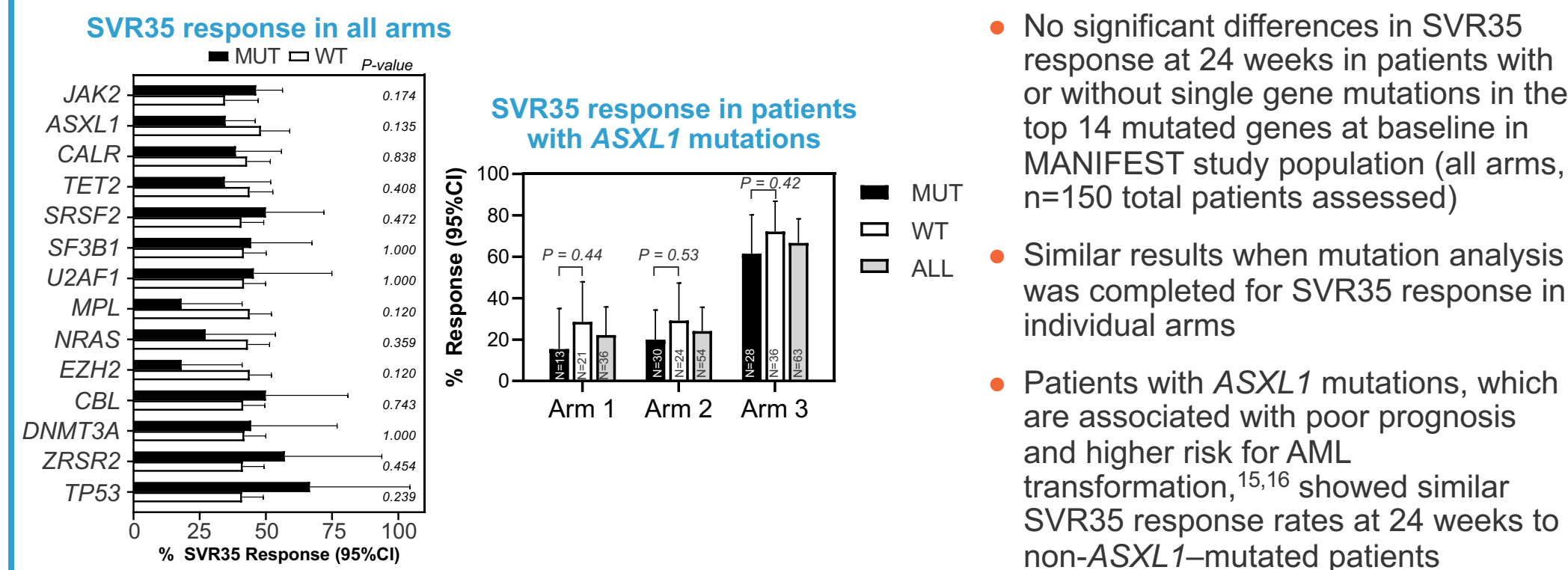
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Baseline Mutation Characteristics of MANIFEST Patients Show Similar Mutation Profiles Across Study Arms



Similar SVR35 Patient Responses at 24 Weeks Irrespective of Baseline Mutation Status of Individual Genes or Study Arm



- No significant differences in SVR35 response at 24 weeks in patients with or without single gene mutations in the top 14 mutated genes at baseline in MANIFEST study population (all arms, n=150 total patients assessed)
- Similar results when mutation analysis was completed for SVR35 response in individual arms
- Patients with ASXL1 mutations, which are associated with poor prognosis and higher risk for AML transformation,^{15,16} showed similar SVR35 response rates at 24 weeks to non-ASXL1-mutated patients

Conclusions

- Pelabresib treatment in all arms rapidly reduced blood *IL-8* (*CXCL8*) gene expression as a PD marker
- Pelabresib and its combination with ruxolitinib reduced levels of cytokines linked to inflammation and NF-κB at an early PD timepoint (14 days) and through Week 24 of treatment
- BM reticulin fibrosis central review shows similar degree of improvement (≥1 grade) to local assessment (37% compared with 33%, respectively) and <7% with worsening fibrosis; improvements also seen in erythroid progenitors and megakaryocyte numbers and clustering, indicating improvements in overall BM function
- Pelabresib both promotes early erythroid differentiation and partially rescues ruxolitinib-mediated suppression of early erythroid differentiation of ex vivo CD34+ progenitor cells from both healthy donors and MF patients
- SVR35 responses seen in all patient arms irrespective of baseline mutation status in single genes, including JAK2, ASXL1 and 12 other recurrently mutated genes in MANIFEST patients
- These data indicate that pelabresib impacts both cytokine expression and BM function and shows broad clinical activity regardless of mutation status; these findings, along with improvements seen in anemia, reticulocytes and hemoglobin (see SOHO 2021 poster number MPN-328), suggest that pelabresib contributes to potential disease-modifying effects in MF