Abstract #483

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Disease-Modifying Activity of Navtemadlin Correlates With Clinical Responses in the Randomized, Multicenter, Global Phase 3 Study BOREAS in JAK Inhibitor Relapsed/Refractory Myelofibrosis

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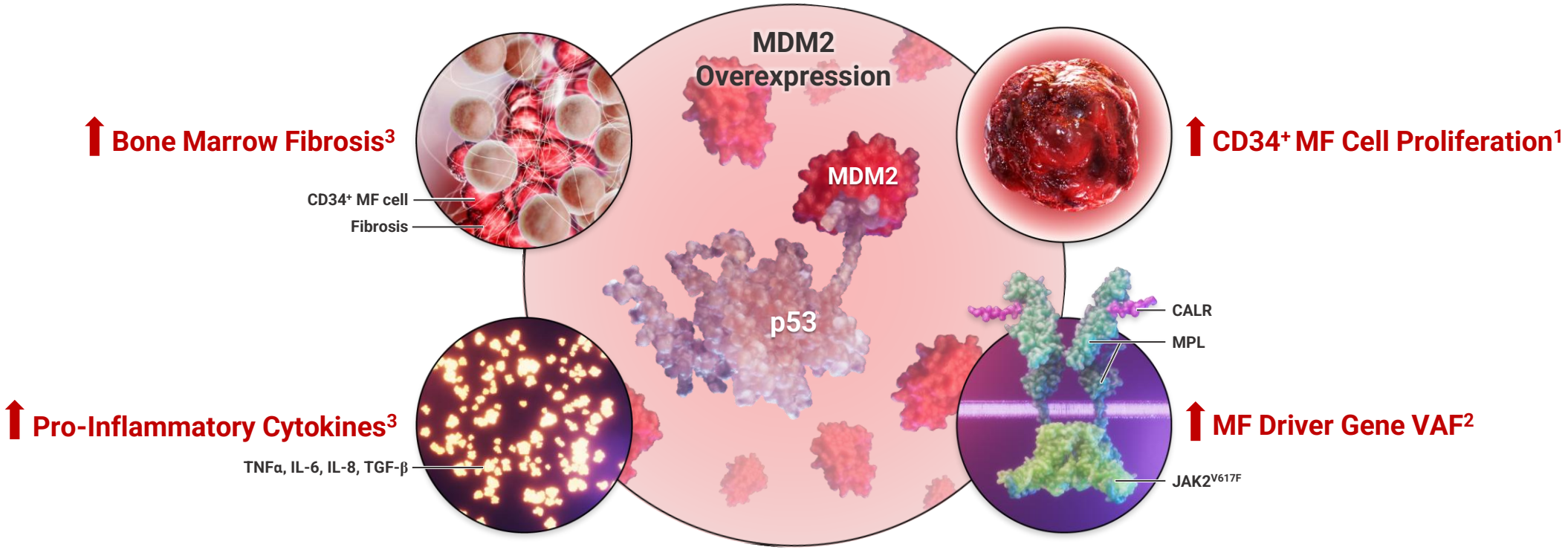
Hallmarks of Myelofibrosis

MDM2 Overexpression Prevents p53-Driven Apoptosis of CD34⁺ MF Cells



[1]Barosi G, et al. *Blood* 2001. [2]Rampal R, et al. *Blood* 2014. [3]Verstovsek S, et al. *NEJM* 2010.
Abbreviations: CALR, calreticulin; IL, interleukin; JAK2, Janus kinase 2; MDM2, mouse double minute 2; MF, myelofibrosis; MPL, myeloproliferative leukemia virus oncogene; TGF-β, transforming growth factor beta; TNFα, tumor necrosis factor alpha; VAF, variant allele frequency.

Navtemadlin is a Novel p53 Potentiating Anticancer Agent

Navtemadlin is a potent, selective, orally available best-in-class inhibitor of MDM2[1,2] that restores p53 function:

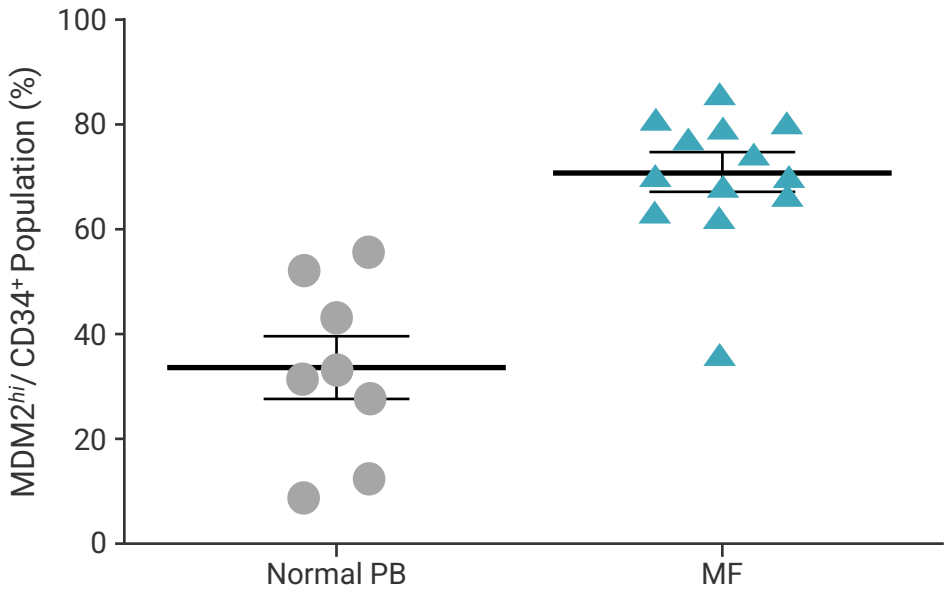
- Binding affinity = 0.045 nM[2]
- IC_{50} = 9.1 nM[2]
- Constant oral clearance across doses[3]
- Rapid absorption (1-3 hour T_{max})[3]
- $T_{1/2}$ = 17 hours[3]

[1]Canon J, et al. *Mol Cancer Ther*. 2015. [2]Sun D, et al. *J Med Chem*. [3]Ma SC, et al. *Blood*. 2019.
Abbreviations: IC_{50}, half maximal inhibitory concentration; MDM2, mouse double minute 2; MPN, myeloproliferative neoplasms; nM, nanomolar; $T_{1/2}$, half-life; T_{max}, time to maximum concentration.

MDM2 Overexpression in Myelofibrosis

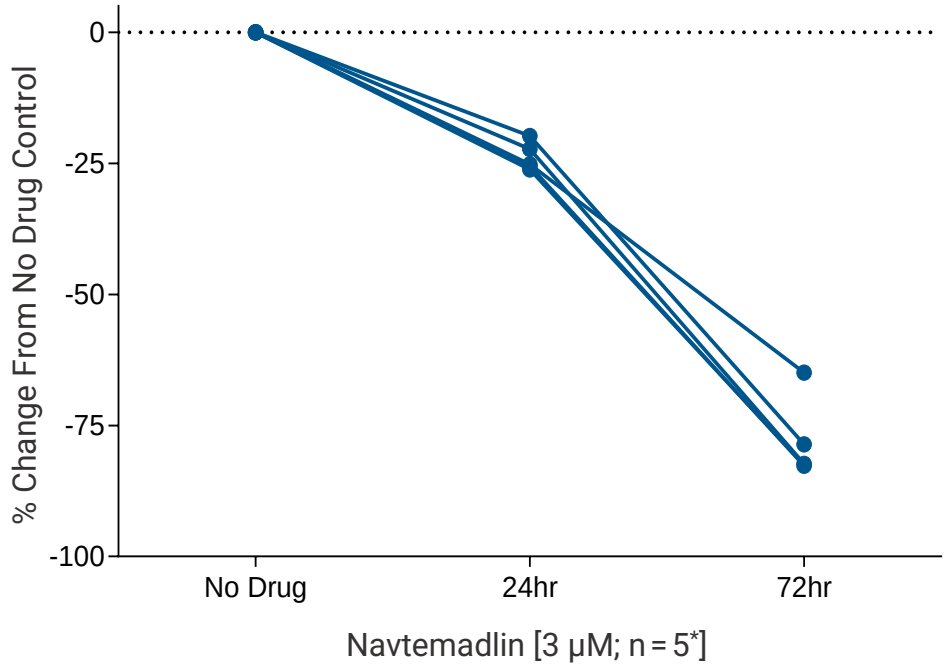
Navtemadlin Induces p53-Dependent Apoptosis of CD34⁺ MF Cells

MDM2 Overexpression in CD34⁺ MF Cells[1]



MDM2 overexpression in circulating CD34⁺ MF progenitors[2]

Navtemadlin Induces Apoptosis of CD34⁺ MF Cells[3]



Navtemadlin induces apoptosis of *TP53*^{WT} CD34⁺ MF progenitors by overcoming MDM2 dysregulation[3]

Note: 95% of MF patients are *TP53*^{WT}.
[1]Figure adapted from Lu M, et al. *Blood* 2017. [2]Nakatake M, et al. *Oncogene* 2012. [3]Clevenger T, et al. EHA 2023.
*CD34⁺ cells collected from MF patients were co-cultured with stromal support layer. Clinically relevant concentrations were used (In vivo C_{max} of navtemadlin = 2.7 µM [~240 mg QD]).
Abbreviations: MDM2, mouse double minute 2; MF, myelofibrosis; PB, peripheral blood; WT, wild-type.

Phase 3 Study Design

A Randomized, Open-Label, Global Phase 3 Study of Navtemadlin in *TP53*^{WT} Subjects With Myelofibrosis Who Are Relapsed or Refractory to JAK Inhibitor Treatment

BOREAS
Blocking MDM2 to reactivate p53 in myelofibrosis

Stratification Factors:
- Primary MF vs Secondary MF
- Baseline TSS (≤10 vs >10)

Physician's Choice (BAT):
- Hydroxyurea
- Peginterferon
- IMiDs
- Supportive care

Patients With JAKi R/R Myelofibrosis

183 Patients

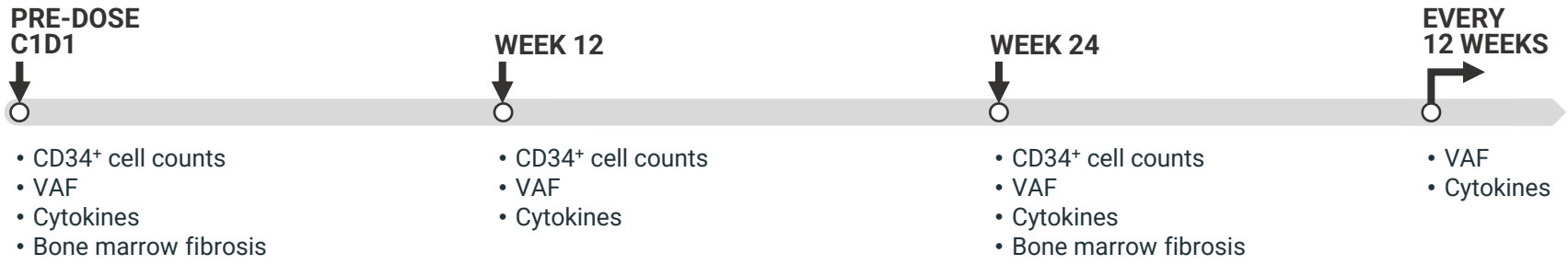
2:1

Navtemadlin 240 mg QD
Days 1-7 / 28-Day Cycle
123 Patients

Best Available Therapy*
60 Patients

1 Cycle = 28 Days

EXPLORATORY ENDPOINTS
- CD34+ cell count in peripheral blood
- Variant allele frequency (VAF)
- Cytokines
- Bone marrow fibrosis



Note: BOREAS enrollment was closed at 183 subjects.
*Crossover permitted in the BAT arm after disease progression or at Week 24.
Abbreviations: BAT, best available therapy; C1D1, cycle 1 day 1; IMiDs, immunomodulatory imide drugs (lenalidomide, pomalidomide); JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; QD, once daily; R/R, relapsed/refractory; TSS, total symptom score; VAF, variant allele frequency; WT, wild-type.

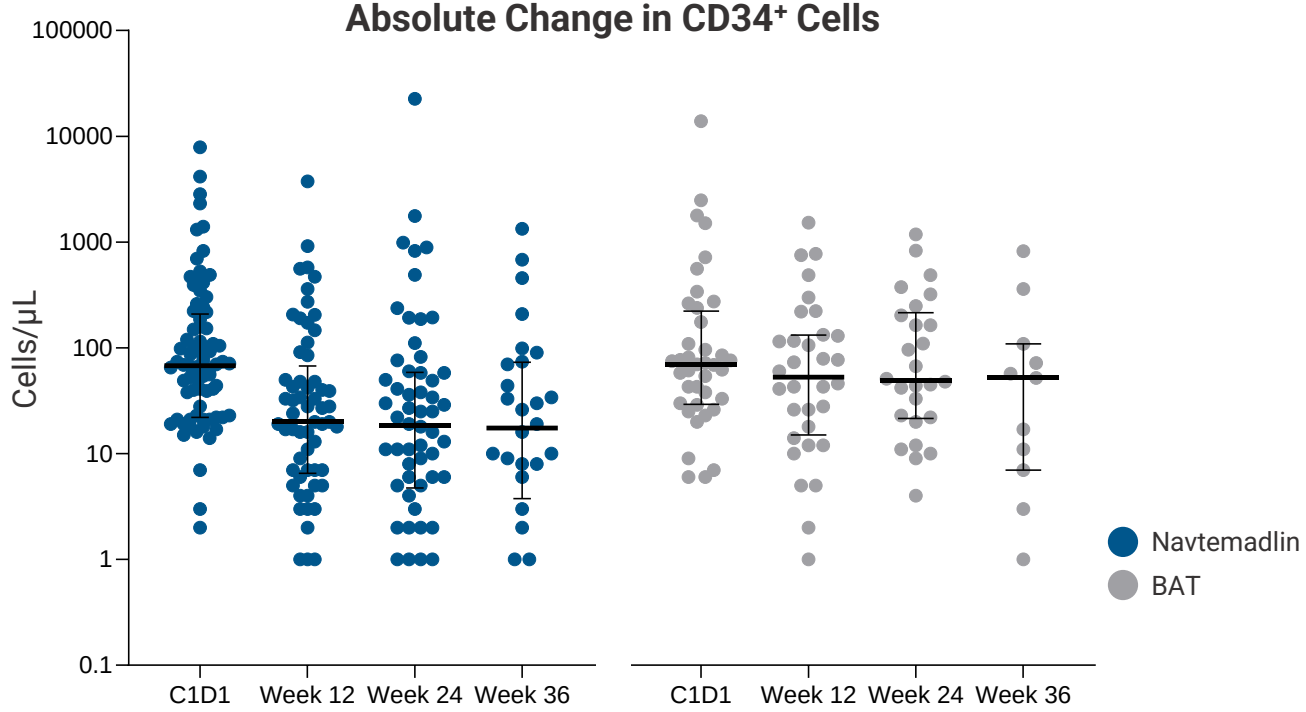
Baseline Characteristics

	Navtemadlin n = 123	Best Available Therapy n = 60[1]
MF Subtype (Primary / Secondary), n (%)	72 (59) / 51 (42)	35 (58) / 25 (42)
JAKi Relapsed/Refractory, n (%)	45 (37) / 78 (63)	21 (35) / 39 (65)
DIPSS (Int-1 / Int-2 / High), n (%)	44 (36) / 60 (49) / 19 (15)	19 (32) / 32 (53) / 9 (15)
TSS, Median (range) TSS > 10, n (%)	20.8 (1.7, 64.3) 94 (76)	20.1 (0, 63.8) 46 (77)
Spleen Volume (cm^3), Median (range)	2321 (184, 5210)[4]	2242 (516, 6002)
Driver Mutations, n (%)		
JAK2^{V617F}	89 (72)	39 (65)
CALR	22 (18)	16 (27)
MPL	5 (4)	1 (2)
Triple Negative	7 (6)	4 (7)
High Molecular Risk Mutations, n (%)[2]		
≥ 1	76 (62)	41 (68)
≥ 2	29 (24)	14 (23)
ASXL1	69 (56)	36 (60)
EZH2	19 (15)	4 (7)
Bone Marrow Fibrosis Score, n (%)[3]		
Grade 1	11 (9)	6 (10)
Grade 2	43 (35)	21 (35)
Grade 3	57 (46)	22 (37)

Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7 / 28-day cycle).
[1]One subject randomized to BAT, first cycle was navtemadlin. [2]HMR included *ASXL1*, *EZH2*, *IDH1/2*, *SRSF2*, *U2AF1*; >3% VAF cut-off.
[3]Samples assessed by central lab (Navtemadlin: n = 111, BAT: n = 49). [4]One subject with baseline spleen volume < 450 cm^3 had palpable spleen ≥ 5 cm LLCM.
Abbreviations: *ASXL1*, additional sex combs like 1; *CALR*, calreticulin; DIPSS, Dynamic International Prognostic Scoring System; *EZH2*, enhancer of zeste homolog 2; Int, intermediate; *JAK2*, Janus kinase 2; JAKi, Janus kinase inhibitor; LLCM, left lower costal margin; MF, myelofibrosis; *MPL*, myeloproliferative leukemia virus oncogene; TSS, total symptom score; VAF, variant allele frequency.

Navtemadlin Reduces Circulating CD34⁺ Cells

Absolute Change in CD34⁺ Cells



Median (cells/µL)	68	20	19	19	70	60	50	52
N	80	61	58	27	38	33	26	11

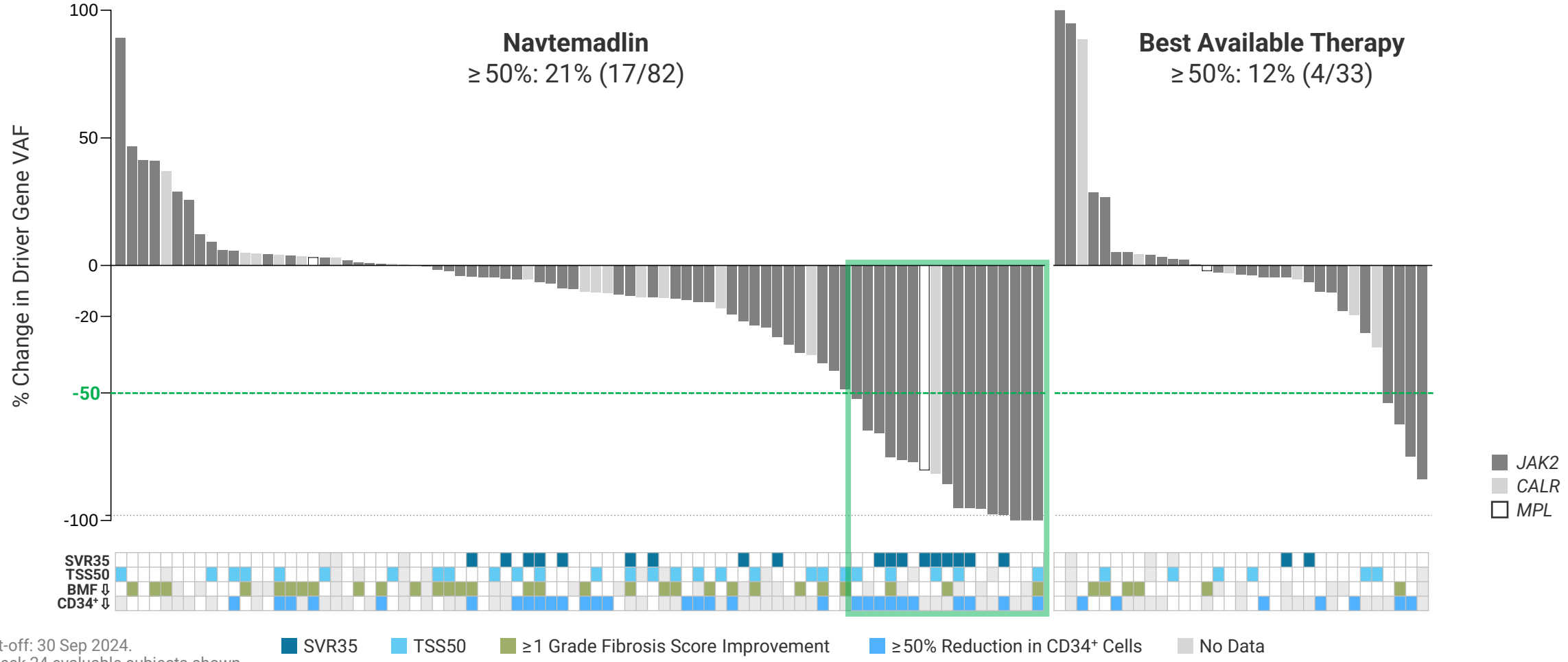
Median % Change CD34⁺ Cells (Baseline Paired)[1]

Median % Change	Navtemadlin	BAT
Week 12	-68% n = 50	-52% n = 25
Week 24	-70% n = 48	-38% n = 19
Week 36	-76% n = 21	-33% n = 9

Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). Peripheral blood CD34⁺ cells normal range ≤ 7 cells/µL.
[1]Required to have a baseline and a second timepoint.
Abbreviations: BAT, best available therapy; C1D1, cycle 1 day 1.

Navtemadlin Reduces Driver Gene VAF

Driver Gene VAF Reduction by Central Laboratory – Baseline to Week 24

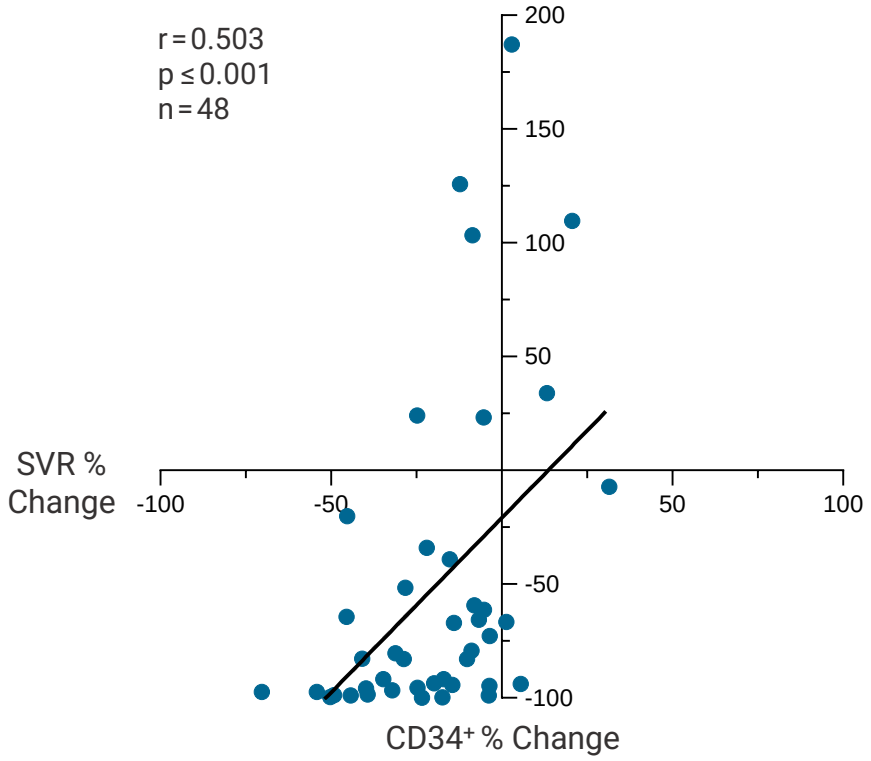


Data cut-off: 30 Sep 2024.
Note: Week 24 evaluable subjects shown.
Abbreviations: BMF, bone marrow fibrosis; *CALR*, calreticulin; *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukemia virus oncogene; SVR35, spleen volume reduction ≥35%; TSS50, total symptom score reduction ≥50%; VAF, variant allele frequency.

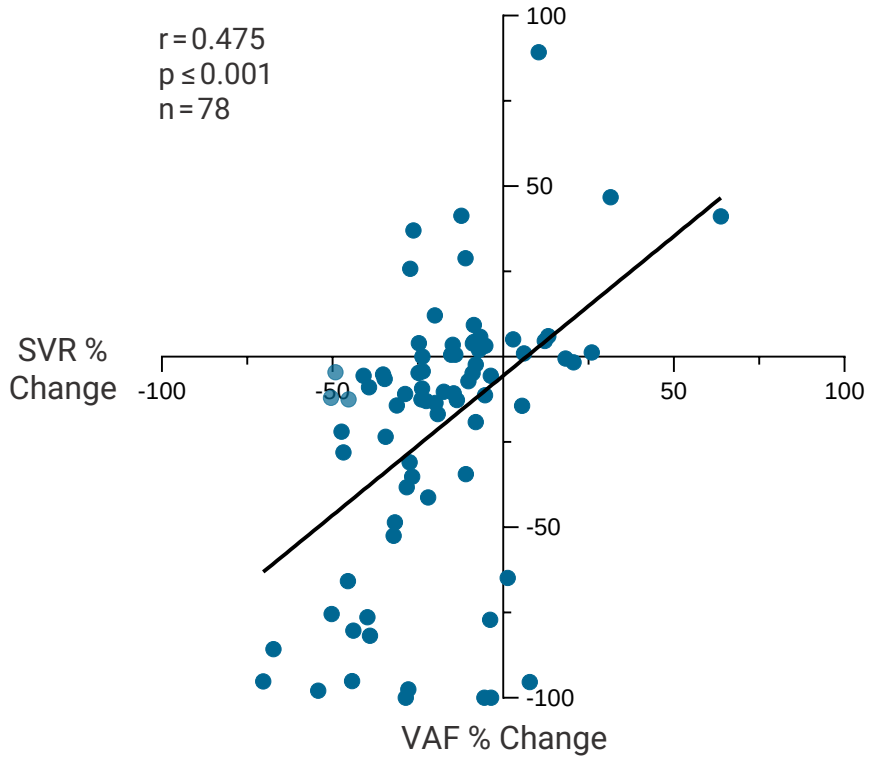
CD34+ and VAF Changes Correlate with SVR

Navtemadlin Reduces Circulating CD34+ and Driver Gene VAF – Baseline to Week 24

Circulating CD34+ Cells at Week 24



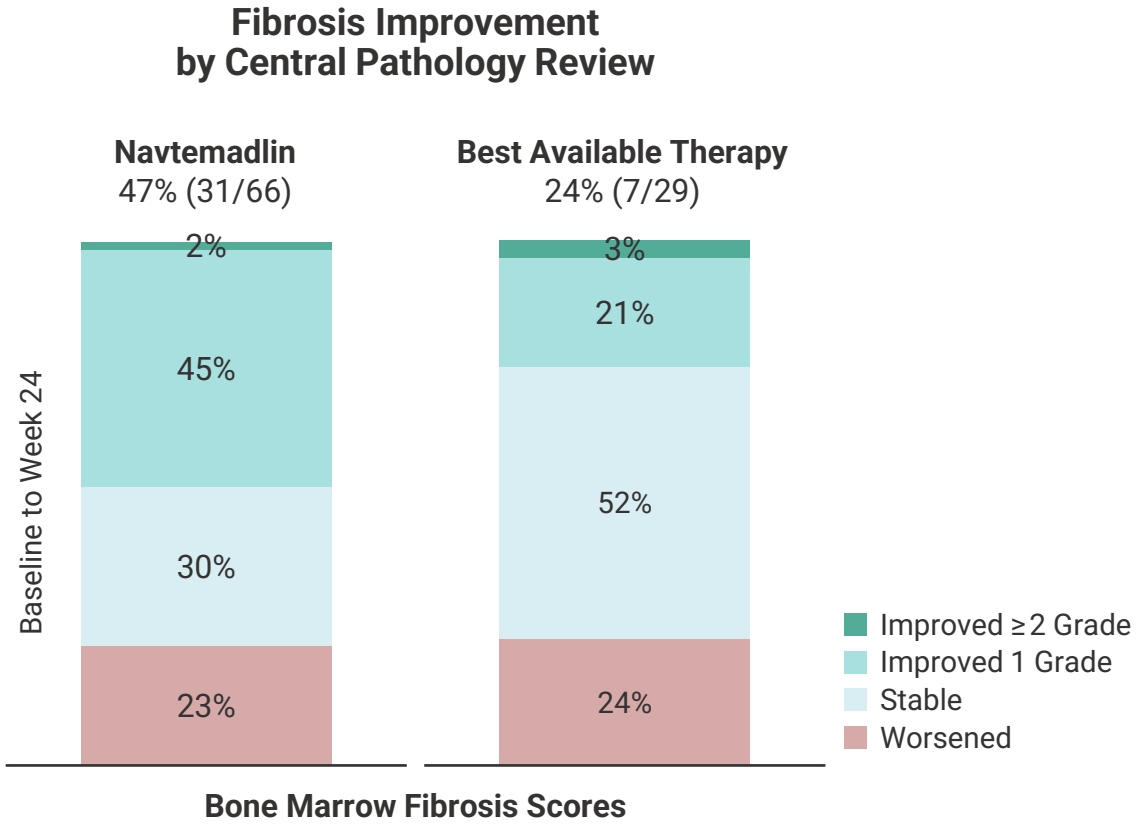
Driver Gene VAF at Week 24

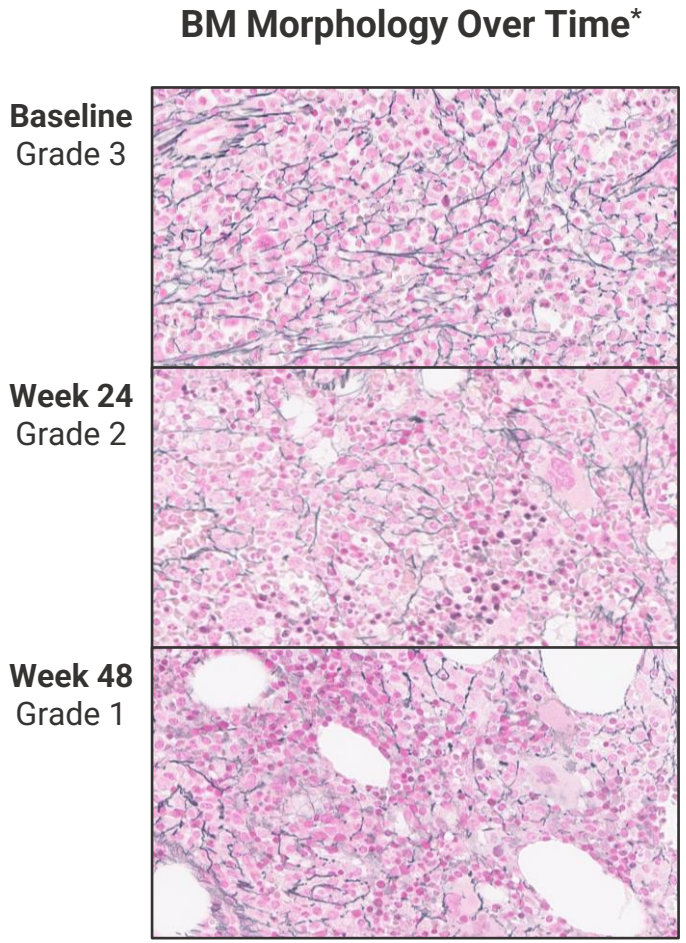


Data cut-off: 30 Sep 2024.
Note: BAT correlations - CD34+ r = 0.521, p = 0.027; VAF r = 0.337, p = 0.069. Baseline to Week 24.
Abbreviations: BAT, best available therapy; SVR, spleen volume reduction; VAF, variant allele frequency.

Navtemadlin Improves Bone Marrow Fibrosis

Bone Marrow Fibrosis Improvement – Baseline to Week 24

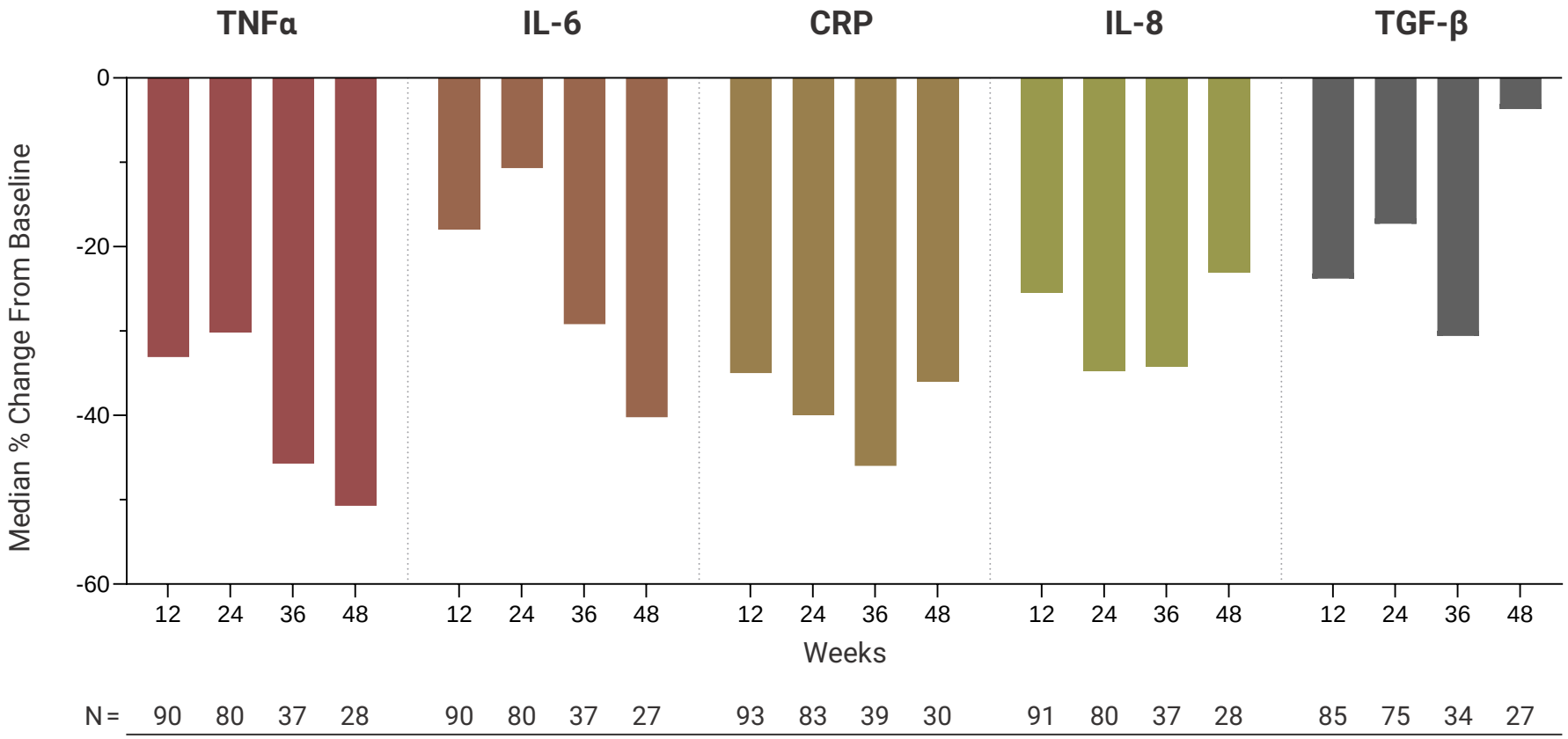




Data cut-off: 30 Sep 2024.
Note: Images at 40X. Baseline to Week 24. *Navtemadlin-treated patient.
Abbreviations: BAT, best available therapy; BM, bone marrow.

Reductions in Pro-Inflammatory Markers

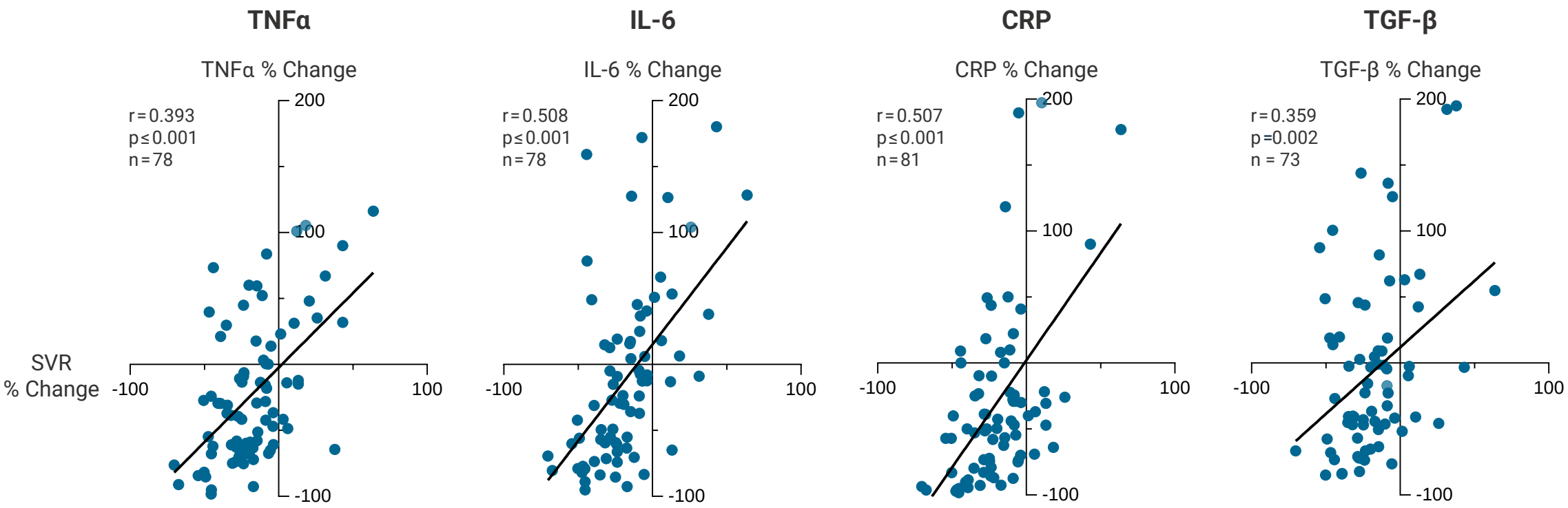
Navtemadlin Reduces Serum Cytokine Levels Over Time



Data cut-off: 30 Sep 2024.
Abbreviations: CRP, C-reactive protein; IL, interleukin; TGF-β, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

Reductions in Inflammatory Markers Correlate With SVR

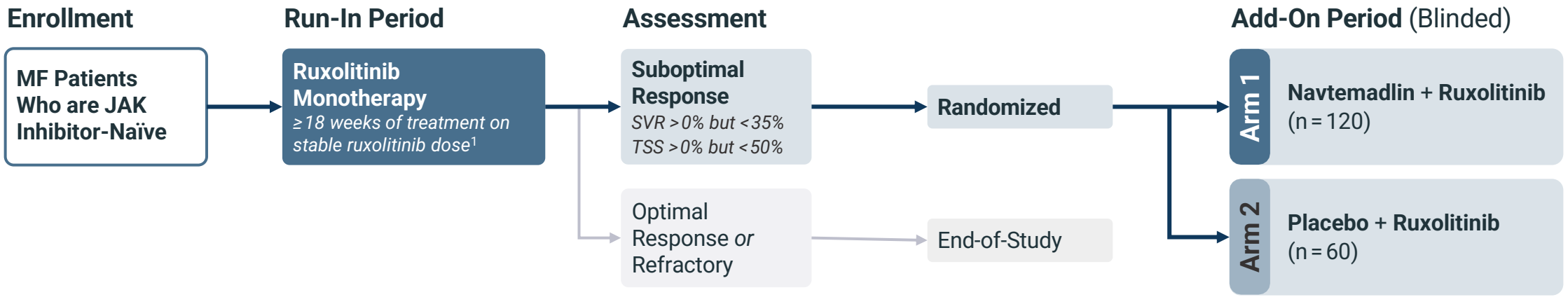
Navtemadlin Reduces Pro-Inflammatory Markers – Baseline to Week 24



Data cut-off: 30 Sep 2024.
Note: BAT correlations - TNFα r=0.372, p=0.051; IL-6 r=0.579, p=0.001; CRP r=0.556, p=0.003.
Abbreviations: BAT, best available therapy; CRP, C-reactive protein; IL, interleukin; SVR, spleen volume reduction; TGF-β, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

Navtemadlin in Suboptimal Responders to Ruxolitinib

A Phase 3 Randomized, Double-Blind, Add-On Study Evaluating the Safety and Efficacy of Navtemadlin and Ruxolitinib vs Placebo and Ruxolitinib in JAK Inhibitor-Naïve Patients With Myelofibrosis Who Have a Suboptimal Response to Ruxolitinib Treatment



Run-In Period (N = 600)

Key Inclusion Criteria

- Primary or secondary MF by WHO criteria
- Int-1, Int-2, or High-risk disease by IPSS
- Spleen volume ≥450 cm^3
- Platelet count ≥100 x 10^9/L

Add-On Period (N = 180)

Key Inclusion Criteria

- *TP53*^{WT} by central testing
- Treatment with a stable dose of ruxolitinib
- Suboptimal response to ruxolitinib run-in

Endpoints

Co-Primary Endpoints

- Targeted SVR and TSS reduction 24 weeks after randomization

Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). Target enrollment from 220 sites across 19 countries.
[1]Stable ruxolitinib is ≥5 mg BID that does not require treatment hold or dose adjustment during the eight weeks prior to add-on navtemadlin or placebo.
Abbreviations: BID, twice daily; Int, intermediate; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; TSS, total symptom score; WHO, World Health Organization; WT, wild-type.

Conclusion

- BOREAS is the first global phase 3 study conducted solely in patients with myelofibrosis who are R/R to JAKi treatment to report results
- Navtemadlin monotherapy improved biomarkers of disease burden in R/R myelofibrosis, suggestive of anti-clonal activity and disease modification
- Navtemadlin-mediated reductions in circulating $CD34^+$ cell counts, driver mutation burden, and serum inflammatory cytokine levels were significantly correlated with magnitude of SVR – a key clinical outcome predictive of quality of life and overall survival
- Biomarkers of disease modification and associated clinical correlations will be further explored with navtemadlin as add-on therapy to ruxolitinib in JAKi-naïve myelofibrosis patients who have a suboptimal response to ruxolitinib treatment (POIESIS; NCT06479135)

Abbreviations: JAKi, Janus kinase inhibitor; R/R, relapsed/refractory; SVR, spleen volume reduction.

Acknowledgments

- We thank all investigators, patients, families, and caregivers who are participating in this study
- We thank Dr. Ronald Hoffman for his pioneering work on MDM2 in myeloproliferative neoplasms
- This study is funded by Kartos Therapeutics, Redwood City, CA
- Editorial and graphics support provided by Cognition Studio, Inc

Navtemadlin
(KRT-232)

Navtemadlin data also presented in
Oral Abstract #1000
TiP Poster #1808.2

Abbreviations: MDM2, mouse double minute 2.