Post ASH San Diego

Myelofibrosis

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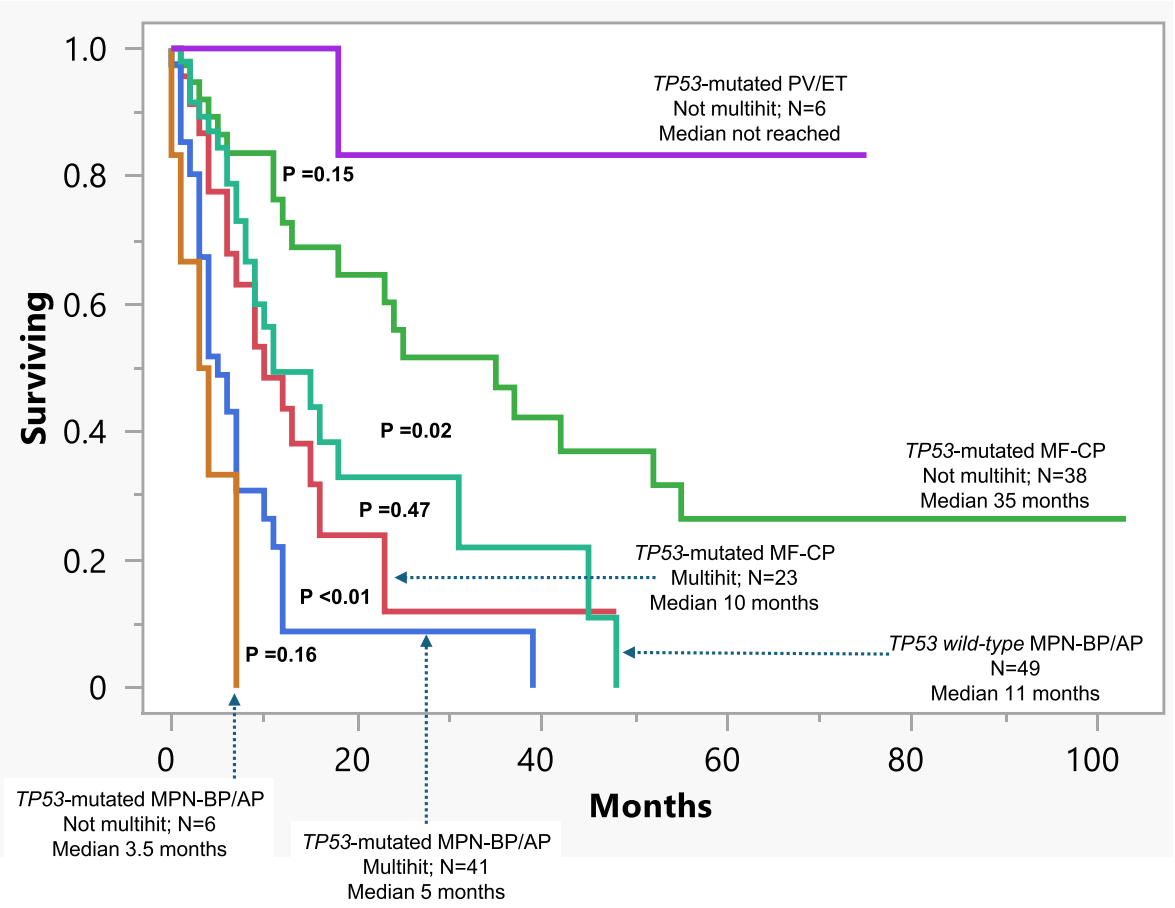
Disclosures

- FRANCESCO PASSAMONTI received honoraria during the last two years for lectures from Novartis, Bristol-Myers Squibb, Abbvie, GSK, AOP Orphan, Jazz and for advisory boards from Novartis, Bristol-Myers Squibb/ Celgene, GSK, Abbvie, Keros, Sumitomo.

- **News on prognostication**

Outcome of 114 Tp53+ MPNs
(CP, 61; BP, 31; AP, 16; PV/ET, 6)

- 65 multihit: BP: 90%; AP: 81%; CP: 39%
- OS in BP/AP was dismal (6 vs. 4.5 mos), regardless of multihit status
- Among BP/AP, OS in *TP53*+ (4 mos) was inferior vs. *TP53* WT (11 mos)
- OS in CP was shorter with multihit versus non-multihit *TP53*+ (10 vs. 35 mos), regardless of MF genetic risk factors with A*SXL1/SRSF2/U2AF1*
- Multihit *TP53*+ associated with inferior survival post SCT



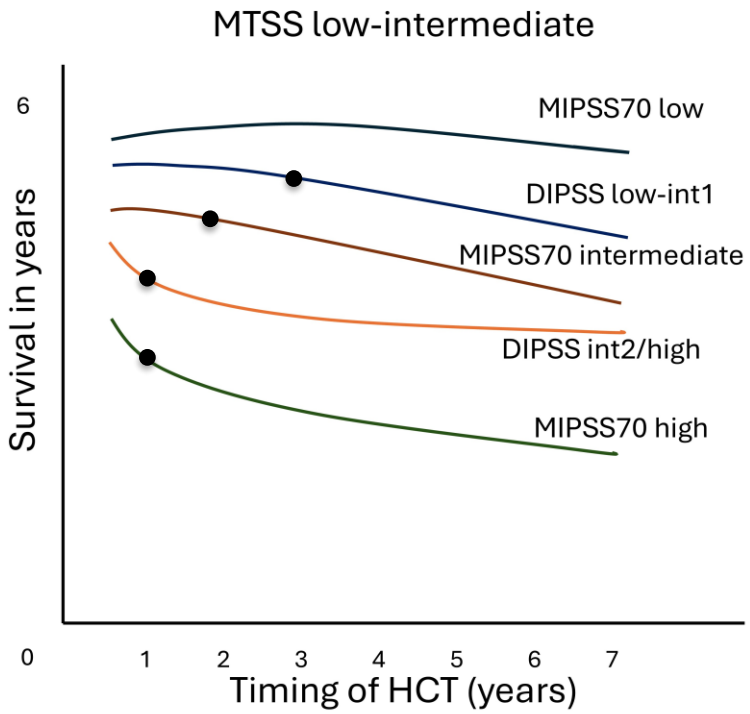
Tefferi et al. Oral at ASH 2024. N 244; AJH 2025

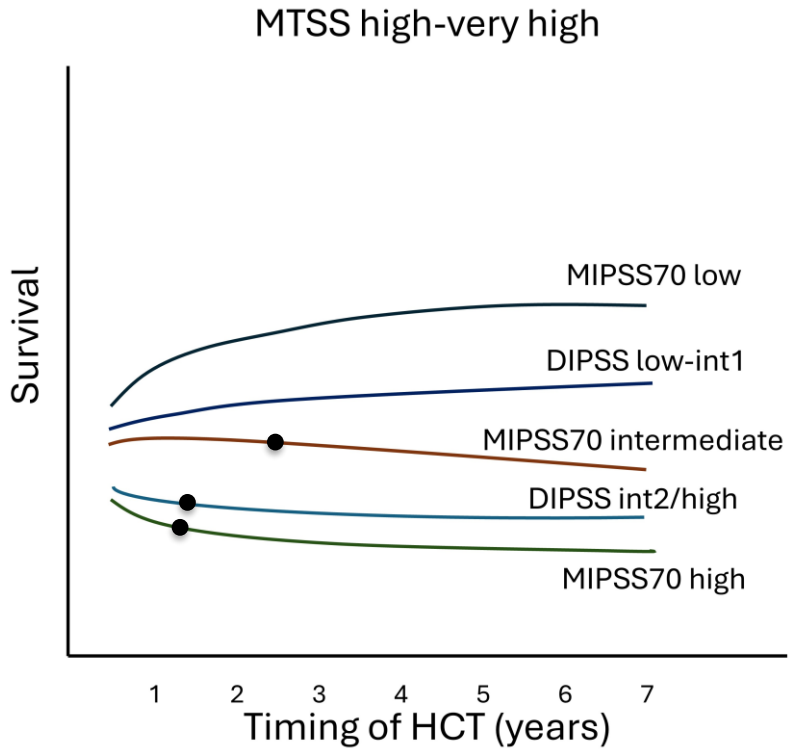
Outcome of 74 Tp53+ MPNs
(ET/PV, 26%, MF, 44%, MDS/MPN, 7%, MPN-U, 3%, MPN-AP/BP, 20%)

- Multi-hit TP53+ was associated with a higher incidence of MPN-AP/BP as compared to single-hit [65% vs 17.5%]
- Compared with HMR mut, multi-hit (HR=2.41) but not single-hit (HR=0.53) TP53+ MPN pts were found to have an increased risk of MPN-AP/BP
- One-year OS from the time of mutation detection was inferior for both configurations of TP53+ as compared to HMR mut (p=<.001)

Handa et al. Oral at ASH 2024. N 243

A multi-state model for timing of SCT in PMF



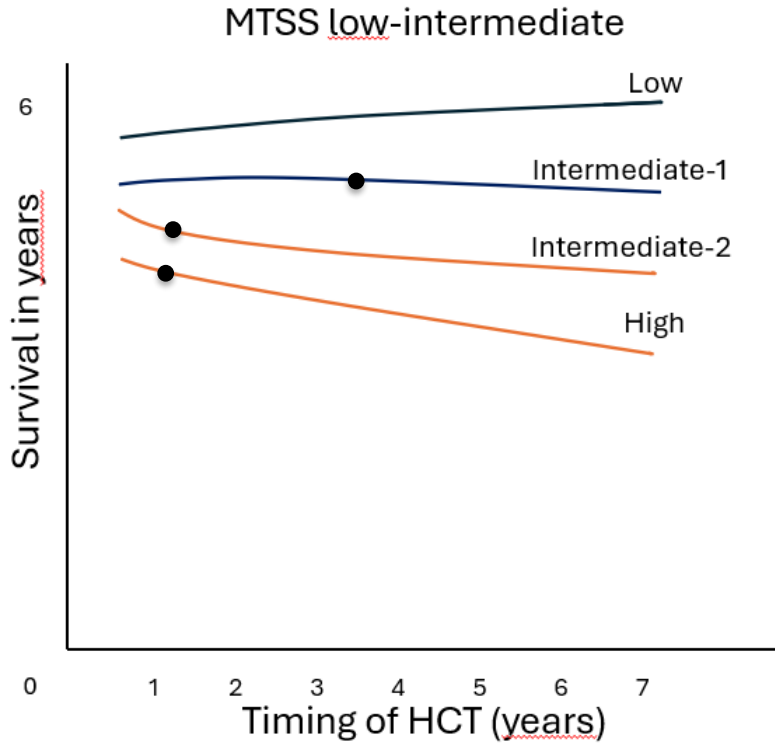


- 3Y for DIPSS low/int-1
- 2Y for MIPSS70 int
- 1Y for DIPSS int-2/high & MIPSS70 high

- Delay HCT by average of 0.5 Y

Gagelmann et al. Oral at ASH 2024. N=245

A multi-state model for timing of SCT in SMF



- Within first 1.5 years for MYSEC-PM int-2/high
- 3.5 years for int-1

For Tp53 MF:
Benefit from early transplantation within 1Y

- Irrespective of disease/risk
- Irrespective of single vs. multi-hit

Gagelmann et al. Oral at ASH 2024. N=245

- **Anti anemia agents**

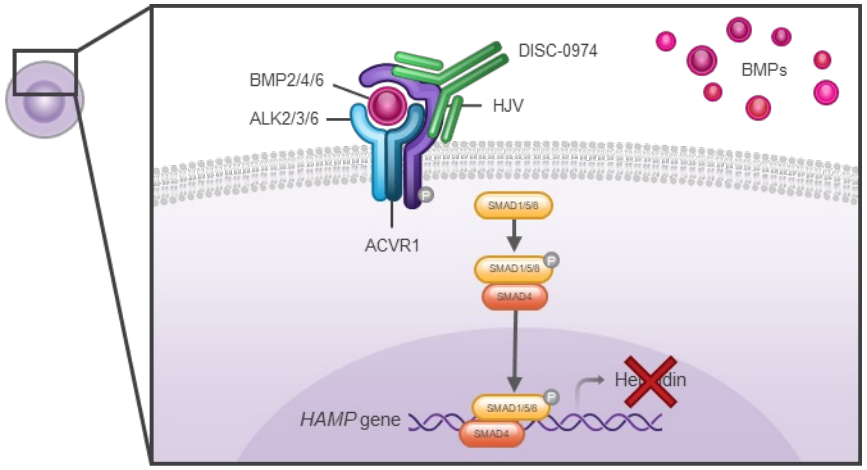
Etiology of Anemia

- High hepcidin from inflammation
- Inflammatory cytokine expression
- Ineffective erythropoiesis
- JAK inhibitors may worsen anemia

Estimated # of Patients

- 25,000 patients (US)
- 64% of patients beyond 1 year of diagnosis have anemia

DISC-0974, a monoclonal antibody binding HJV and blocking BMP signaling. A phase 1b Study on 35 pts



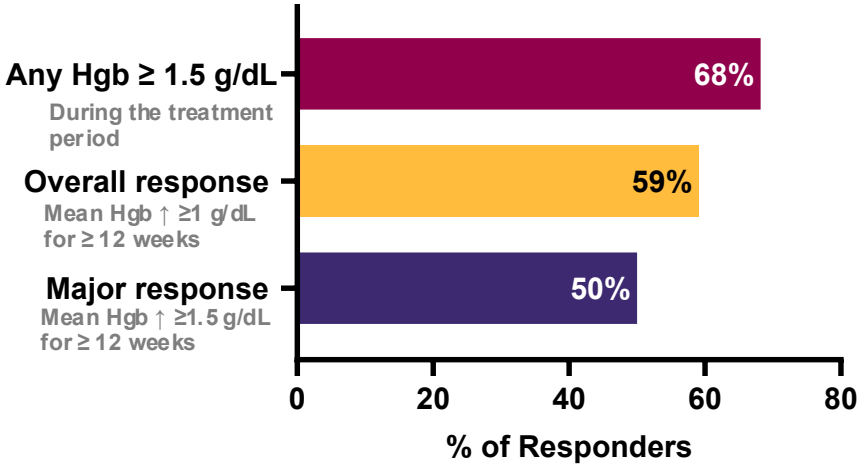
- Reduce Hepcidin production
- Increase Iron absorption
- Increase Mobilization of stored iron into circulation
- Increase Hgb levels

- Int-2 or high-risk disease MF
- Hemoglobin <10 g/dL on ≥3 assessments over 84 days (N=23) or TD (N=12)
- Concomitant stable JAK inhibitor (N=13) or hydroxyurea (N=4)
- Results for 28-100 mg cohorts

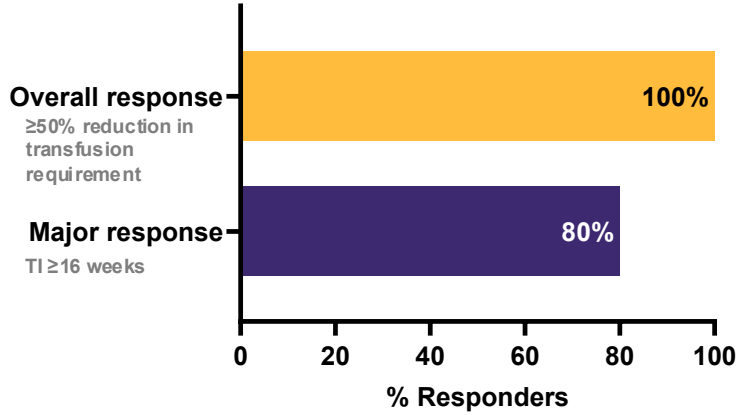
Naseema Gangat et al. Oral at ASH 2024. N=657

Hematologic Response of DISC-0974

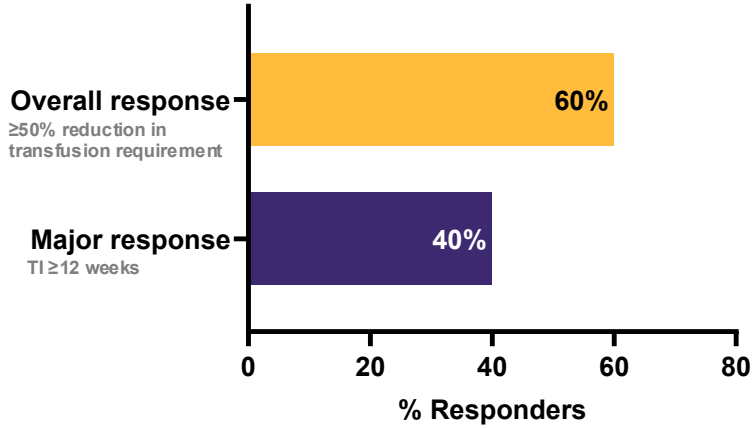
Non-Transfusion-Dependent Participants (n=22)

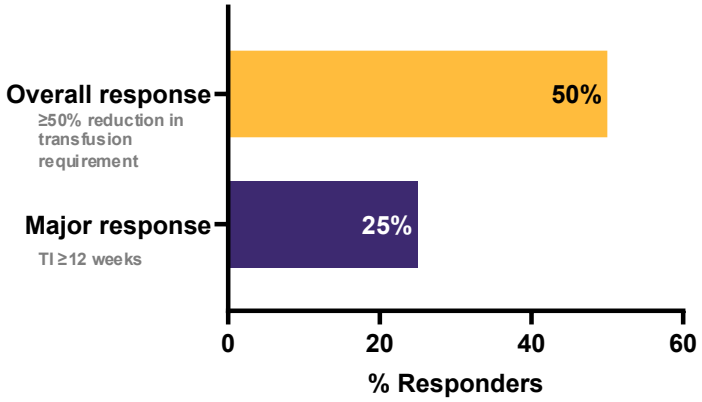


Transfusion-Dependent-Low Participants (1-2) (n=5)



Transfusion-Dependent-High Participants (3-12) (n=5)





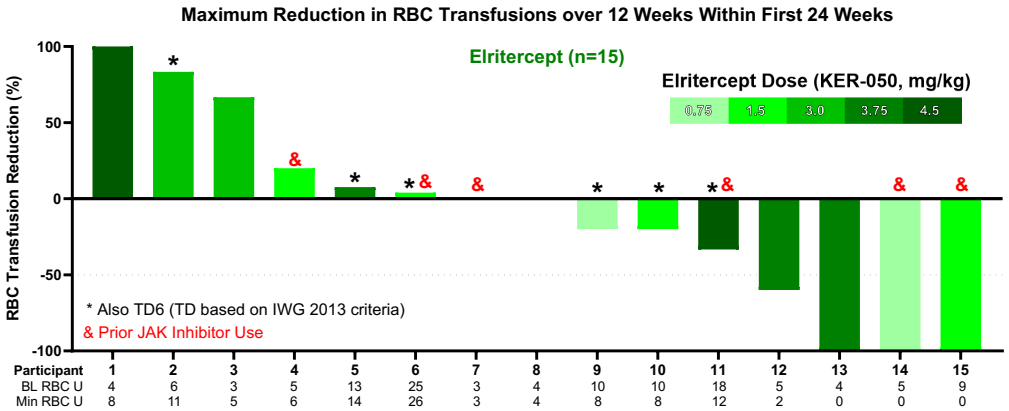
Hematologic Response with Concomitant JAKi Therapy (n=13) in TD-High Response (n=4)

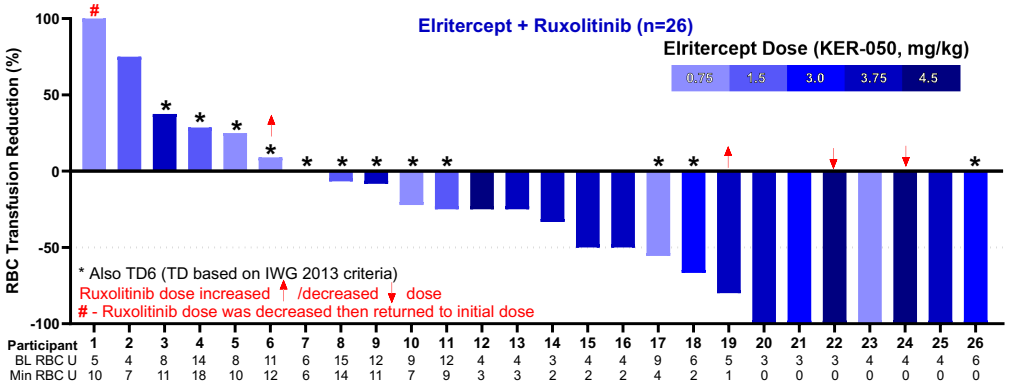
Naseema Gangat et al. Oral at ASH 2024. N=657

Elritercept, inhibitor of select TGF-beta superfamily ligands, including activin A

phase 2 RESTORE Study

70% receiving ≥ 3 RBC U/12W
63% had BL SV≥ 450 cm^3 (66% of those on RUX)
73% with meaningful baseline symptom scores





- Transfusion burden in TD3 In both arms
  - 16/41 (39%) had reduction ≥ 50%
  - 10/41 (24%) achieved TI
- Transfusion burden in TD3 in RUX+Elri (>=3 mg/kg)
  - 10/16 (62.5%) had reduction ≥ 50%
  - 6/16 (37.5%) achieved TI

- Reductions in spleen size in both arms
  - 8/20 (40%) had reduction ≥ 10%
  - 3/20 (15%) had reduction ≥ 35%

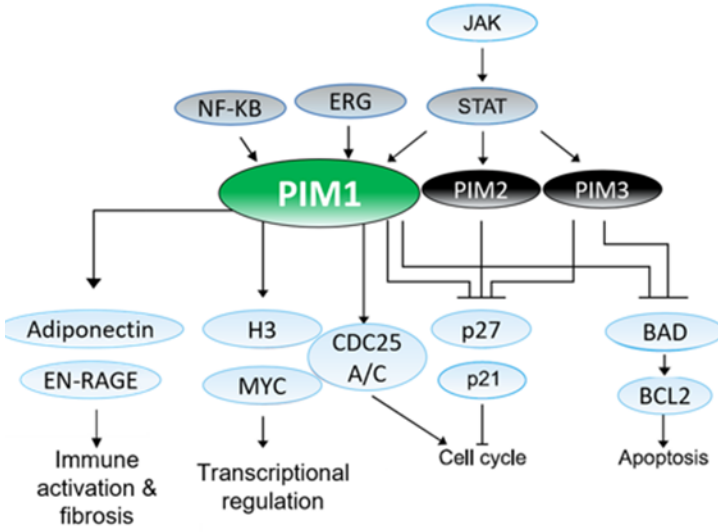
- MF-SAF-TSS symptom scores
  - Reduced in 18 of 27 (67%)

Claire Harrison et al Oral at ASH 2024. N=997.

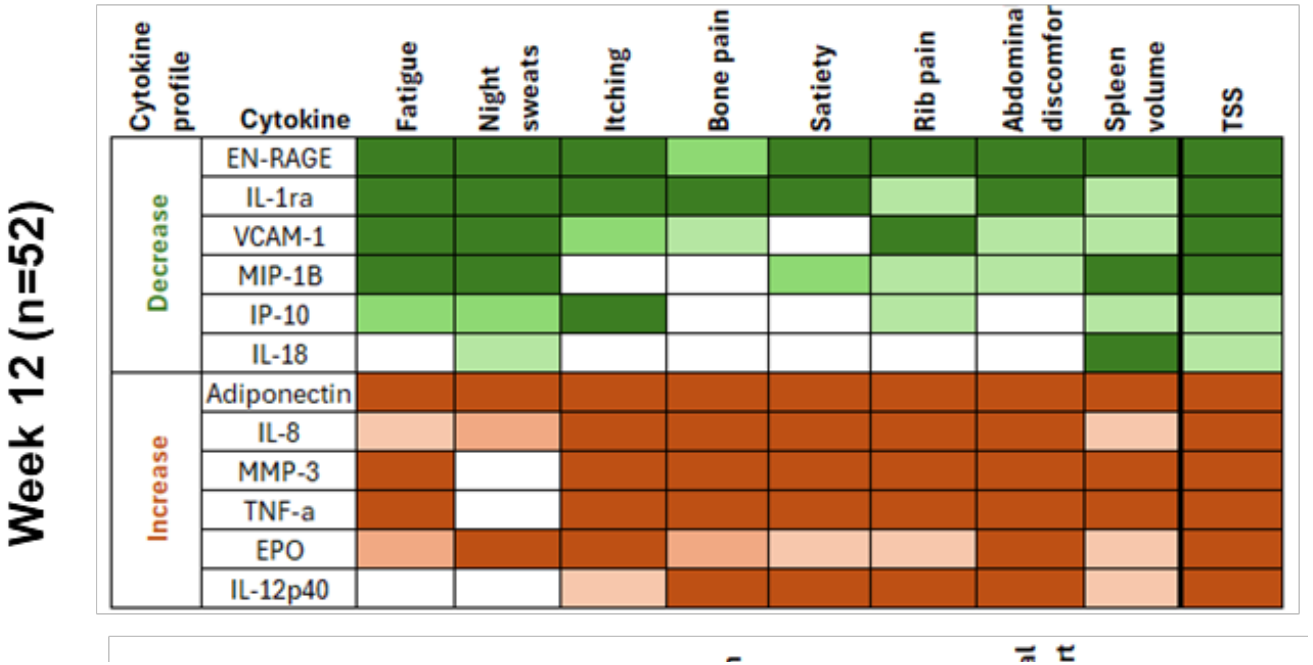
- New non JAKi agents

Nuvisertib (TP-3654), a selective PIM1i Phase 1/2 Study in 74 R/R/I/I MF

PLT count ≥ 25 x 10%/L
Spleen size:13 cm; TSS 24
DIPSS int2/HR 77%
RBC TR: 30%
28/74 on active treatment



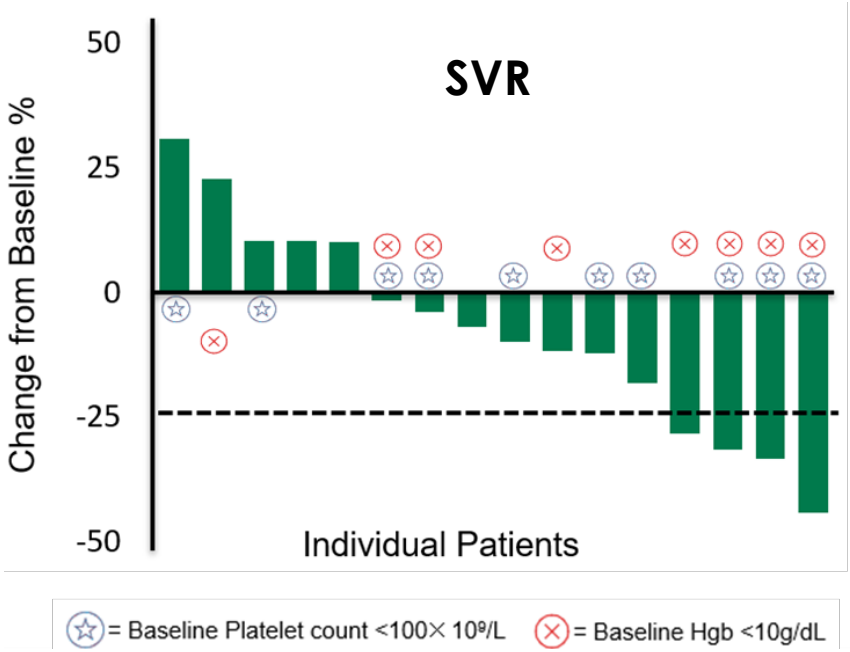
- PIM1 is regulated in part through JAK/STAT, NF-Kappa B, ERG pathways, and its upregulation leads to cytokine modulation relevant to immune activation and fibrosis



ENRAGE and adiponectin levels were significant predictors of SVR, TSS50 responses

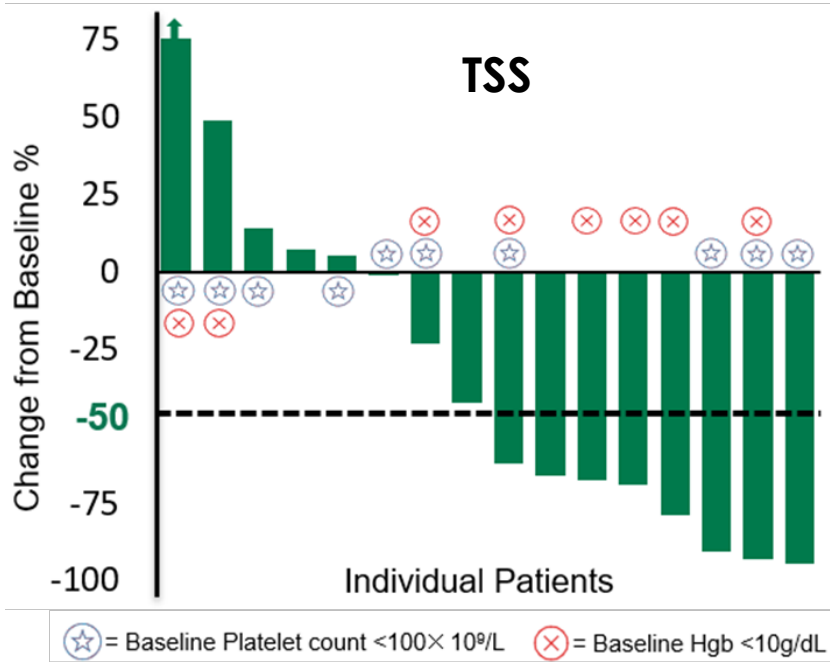
Firas El Chaer et al. et Oral at ASH 2024. N=655: Lindsay Rein at ASH 2024. N=3179

Nuvisertib responses at 720 BID (RP2D)



11 of 18 (61%) with SVR

4 of 18 (22.2%) with SVR25



8 of 18 (44%) with TSS50

- Hb remains overall stable
- 6/24 (25%) had mean ≥1.0 g/dL Hgb increase without any RBC transfusion
- 8/29 (27.6%) with ≥ 30x10(9)/L platelet increase without PLT transfusion
- 11/23 (47.8%) with ≥ 1 grade BMF improvement

Firas El Chaer et al. Oral at ASH 2024. N=655

INCB057643, a BETi, in R/R MF patients and other advanced myeloid neoplasms

Results from a Phase 1 Study

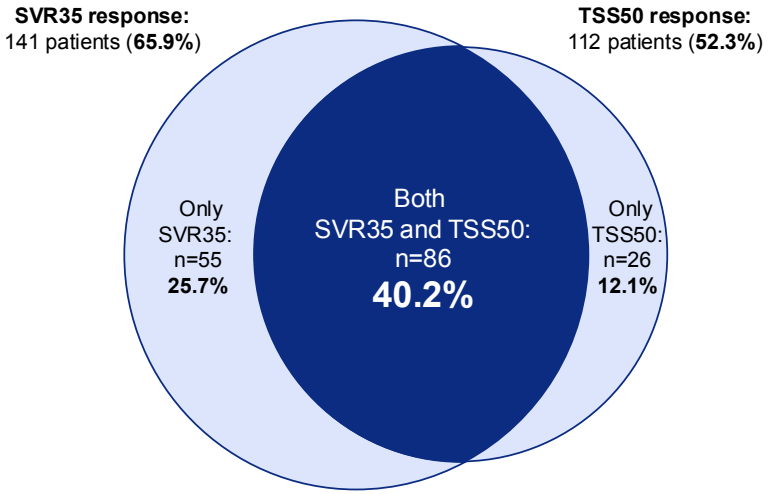
- SVR
  - SVR35 with monotherapy in 3/7 among those on INCB057643 ≥10 mg
  - SVR35 with Combo in 4/17
- TSS
  - TSS50 in monotherapy in 5/8 among those on INCB057643 ≥10 mg
- Anemia
  - 6/22 (27%) in monotherapy and 4/20 (20%) in combo achieved anemia response (>1.5 g/dL hemoglobin increase (TI) and TI (TD)

Justin Watts et al. Oral at ASH 2024. N=658

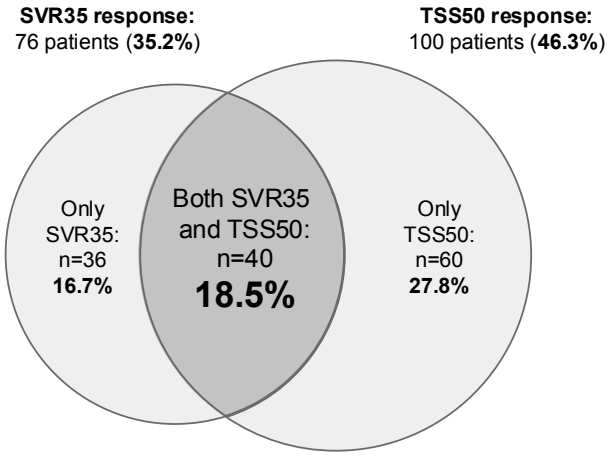
Pelabresib (BETi) + RUX *vs.* RUX (1L) (MANIFEST-2)

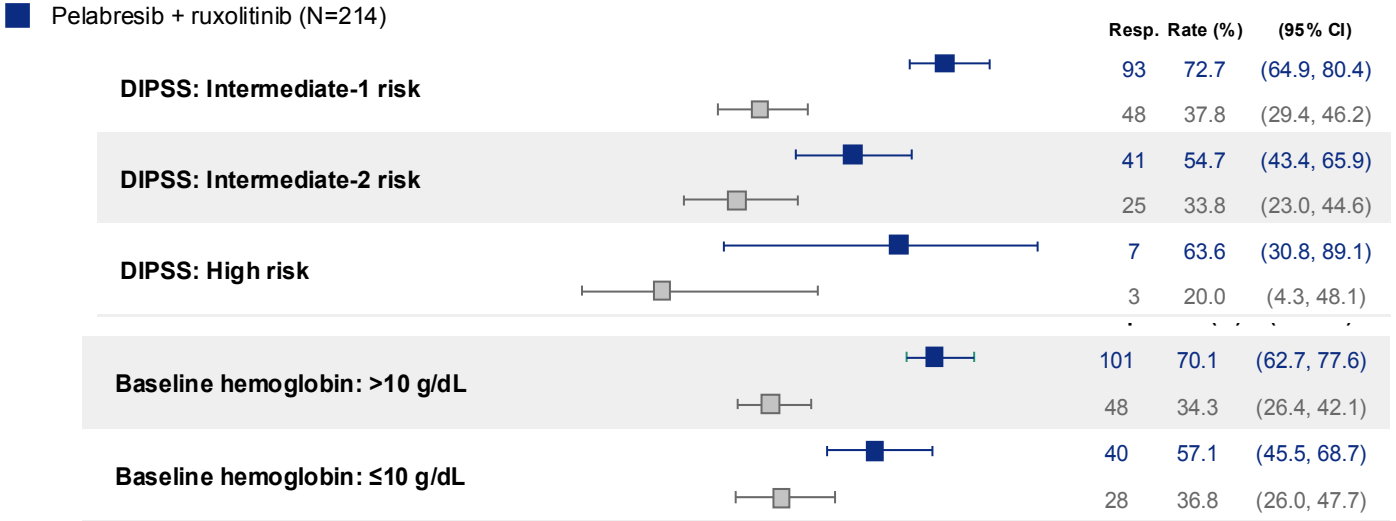
- SVR35: 66% *vs.* 35%
- SR loss: 13% *vs.* 28%
- TSS50: 52% *vs.* 46%
- TSS change: -15.9 *vs.* -14
- Hb response in anemic: 16% *vs.* 14%
- RBC-TI: 11% *vs.* 10%
- BMF >=1G: 38% *vs.* 25%

Pelabresib + ruxolitinib (N=214)



Placebo + ruxolitinib (N=216)

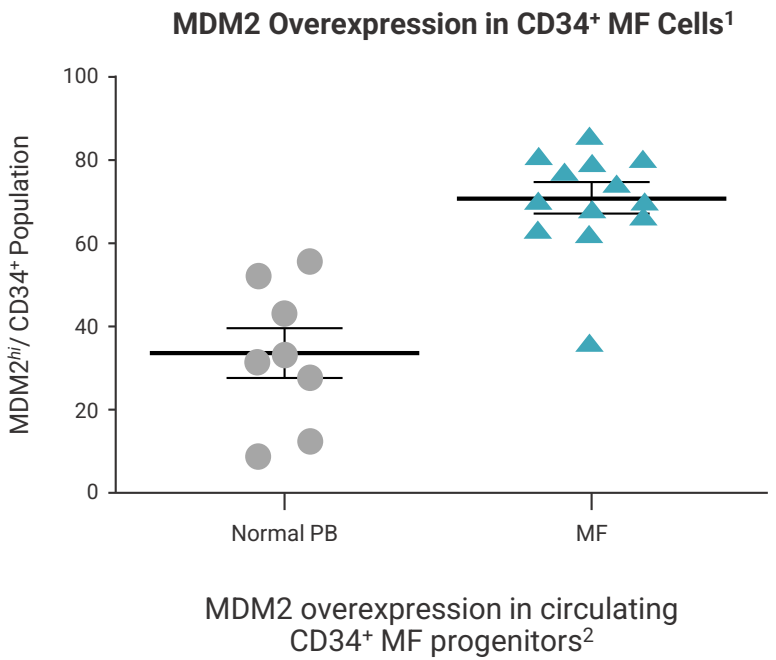




Accelerated and blast phase	3.3	2.3
Accelerated phase	0.9	1.9
Blast phase	2.4‡	0.5

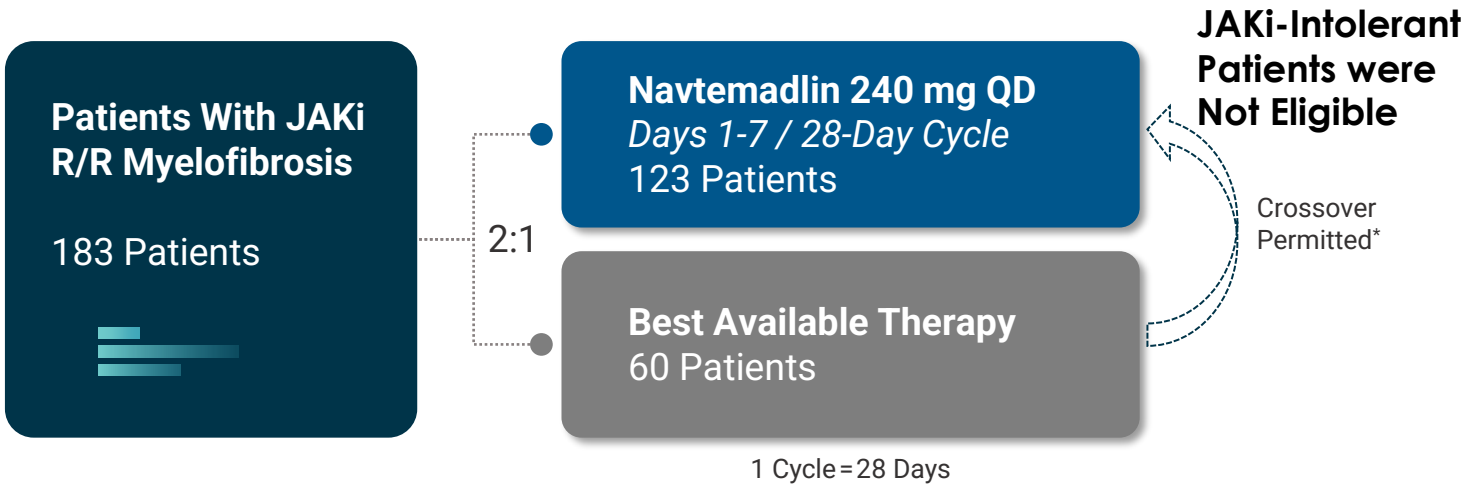
Raajit K. Rampal et al Poster at ASH 2024. N=3178

Navtemadlin, a MDM2i p53 potentiating agent BOREAS study in MF



- Navtemadlin induces apoptosis in TP53WT CD34+ MF progenitors by overcoming MDM2 dysregulation

BOREAS: A Randomized, Open-Label, Global Phase 3 Study of Navtemadlin in TP53WT Patients With Myelofibrosis Who Are Relapsed or Refractory to JAKi1

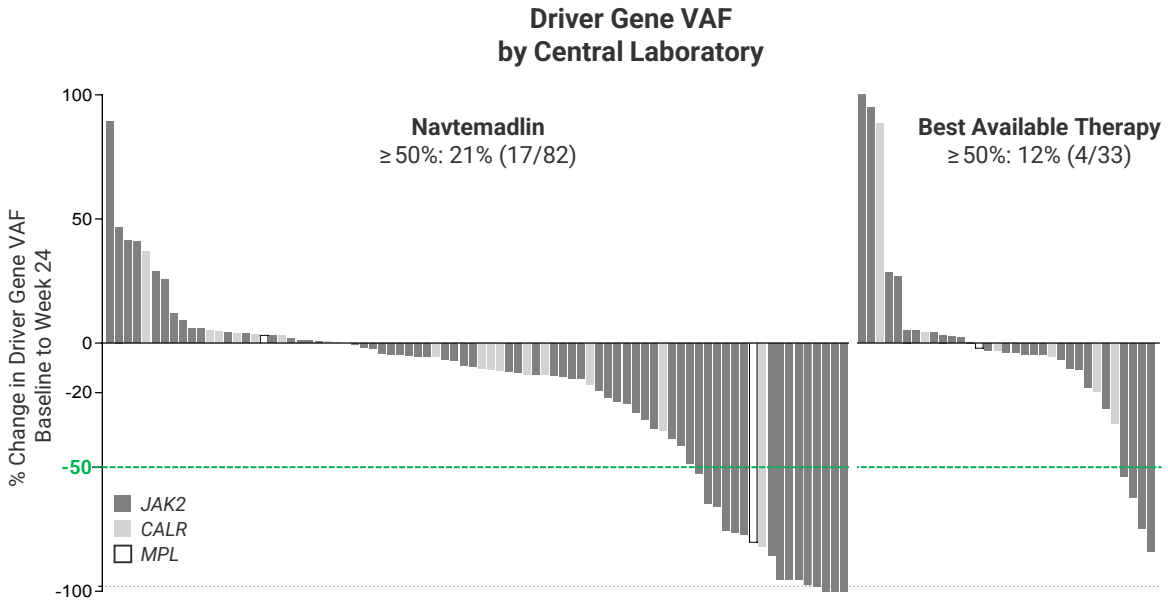


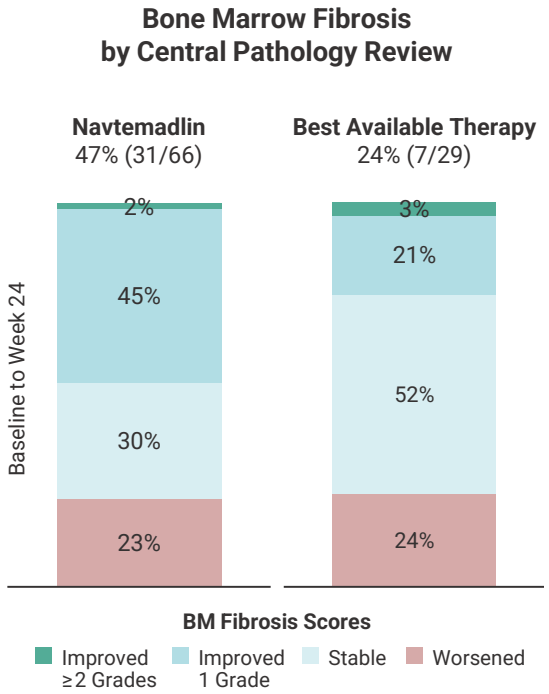
DIPSS int-2/HR 64%
TSS 20
TD anemia 21%
HMR: 62%

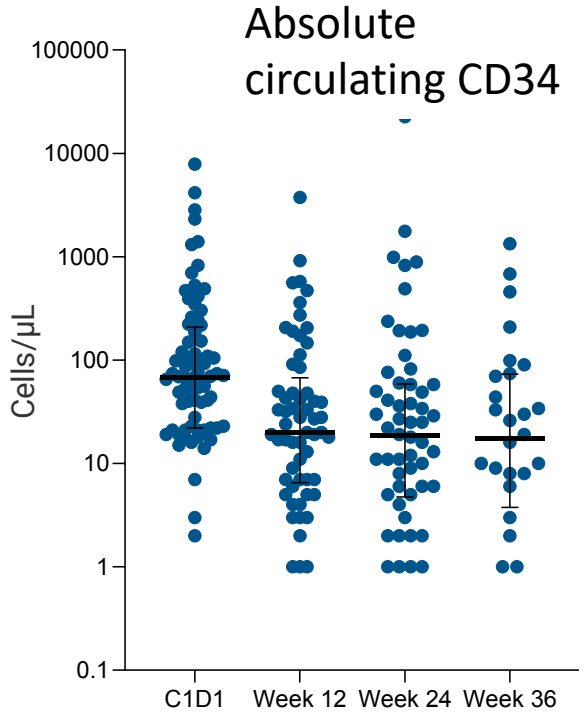
Nakatake M, et al. Oncogene 2012; Clevenger T, et al. EHA 2023; 386820. Abstract P991; John Mascarenhas et al. Oral at ASH 2024. N=1000

BOREAS: driver gene VAF reduction BMF improvement and CD34 reduction at W24

SVR35: 15% vs. 5%
TSS50 24% vs. 12%
BP: 1,6% vs 3.3%







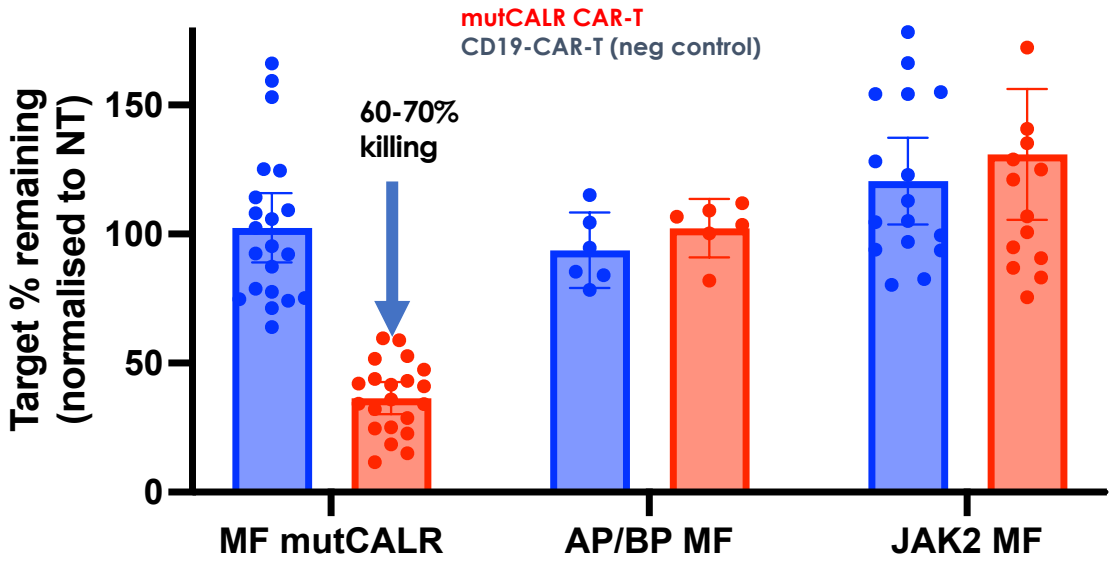
Data cut-off: 30 Sep 2024.
Note: Week 24 evaluable subjects shown.
Abbreviations: BM, bone marrow; *CALR*, calreticulin; *JAK2*, Janus kinase 2;

- CD34+ and VAF changes correlate with SVR
- TP53MUT subclones detected on study in 19%, all pre-existing at baseline

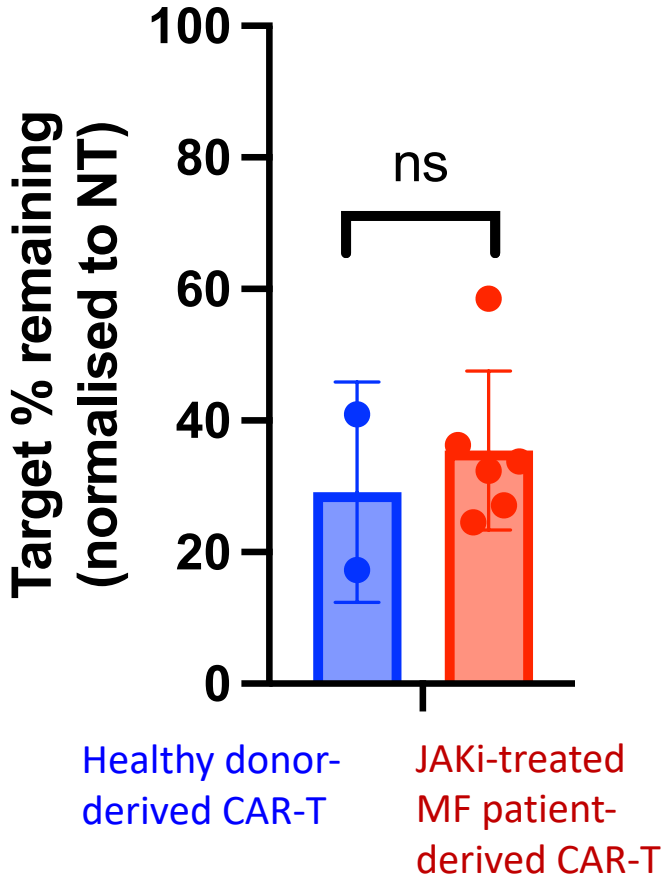
John Mascarenhas et al. Oral at ASH 2024. N=1000 & 483

CALRmut: CAR-T selectively targets HSCT in vitro & in vivo

- Selective killing of mutCALR CD34+ cells from patients with mutCALR MPNs
- No killing of accelerated/blast phase MPN CD34+ cells - due to low expression of TPO-R



- CAR-T generated from patients on JAK inhibitors are efficacious



Alexandros Rampotas et al. Oral at ASH 2024 N=871

Other targets

- Imetelestat+RUX (IMproveMF) combo in 2L was safe with IME dose-dependently effective
- Fedratinib in the FREEDOM2 trial (2L) showed early increases in PLT count versus BAT
- Rovadicitinib, a JAK/ROCKi, reached in 8 pts (2L) SVR35 (75%), TSS50 (50%) on study period
- Selinexor + RUX in 2L (p2) reached in 25 pts SL50 (40%), TSS50 (40%), and TI from TD (55%)
- Flonoltinib Maleate, highly selective to JAK2 by simultaneously binding to the JH2 and JH1 achieved in 30 pts in 2L the best SVR35 in 83.3% and the best TSS50 in 80.0%
- CXCR4/CXCR12 axis might contribute to suboptimal therapeutic efficacy of RUX, by deregulation of inflammatory pathways. CK0804 Treg, a cord blood-derived CXCR4 enriched T regulatory cells, was safe and effective in R/R MF (up to 6 fixed dose of 100 million cells, added every 28 days to steady dose ruxolitinib)

John Mascharenhas et al. Oral at ASH 2024. N=998; Catherine Al-Ali et al. Oral at ASH 2024 N=482; Chunkang Chang et al. Oral at ASH 2024 N=484; Minghui Duan et al Oral at ASH 2024 N=1002; Lijuan Chen et al. Oral at ASH 2024 N=486; Lucia Masarova et al. Oral ar ASH 2024 N=999

Conclusions on main topics at ASH 2024 in MF

- Prognostication
- Anti anemia agents
- New targets