New drugs in myelofibrosis

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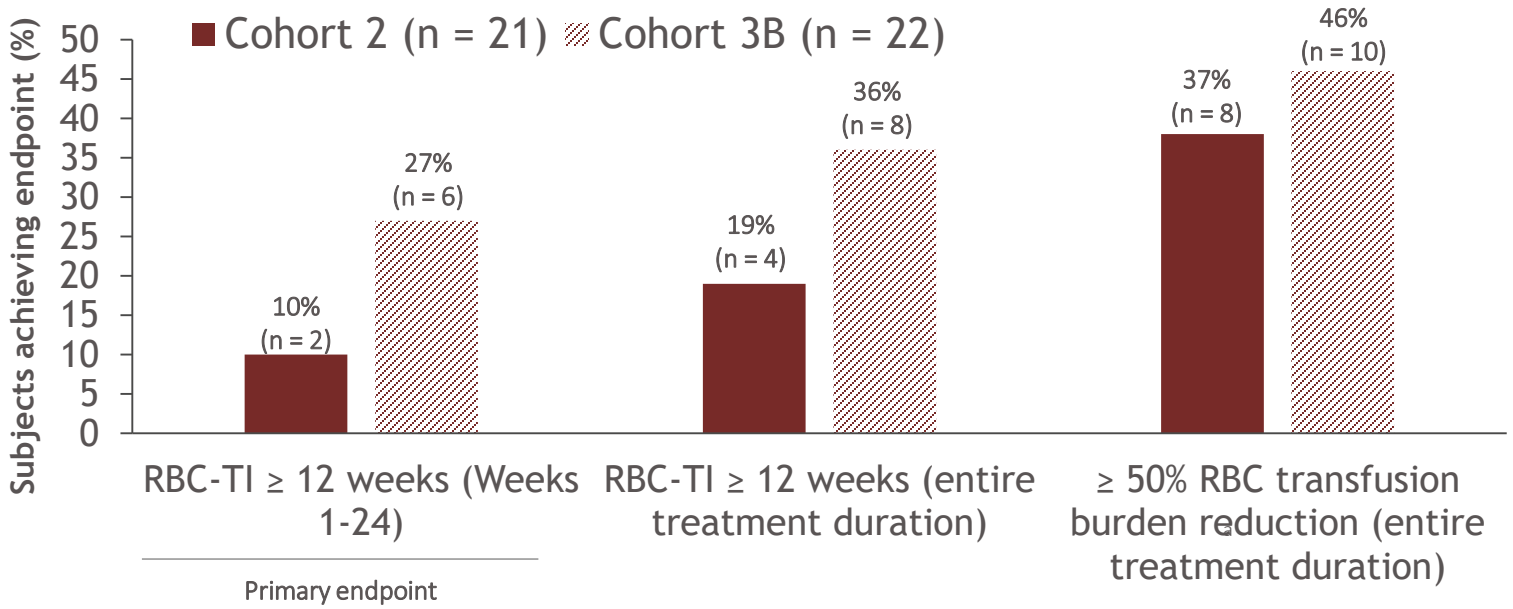
Disclosures

- F Passamonti: honoraria for lecture and advisory boards from Novartis, Celgene, Bristol-Myers Squibb, Abbvie, Janssen, Roche, AOP Orphan, Karyiopharma, Kyowa Kirin and MEI; grants for research project from BMS

- Unmet medical need: anemia

Luspatercept response in MF patients who are RBC-TD Phase 2, ACE-536-MF-001 trial

- Cohort 2: No-RUX, RBC-TD ; Cohort 3B: RUX, RBC-TD



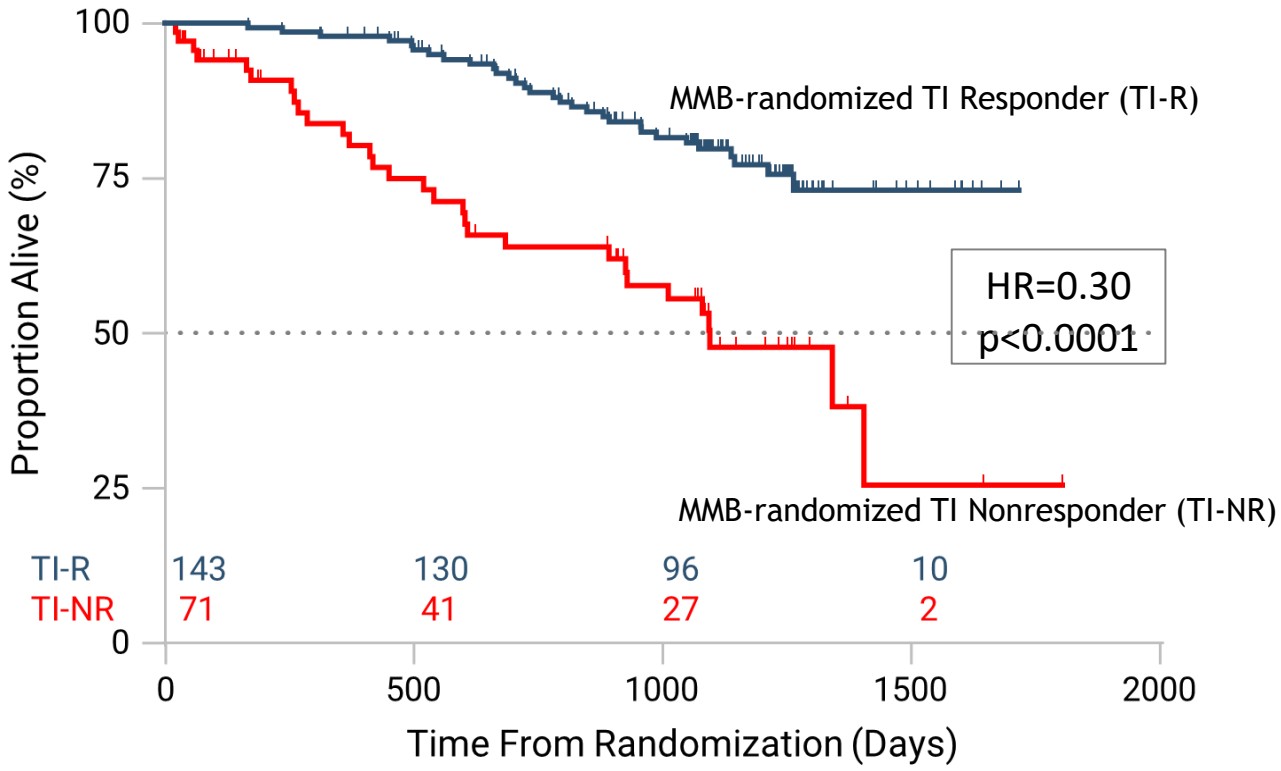
[a]Defined as RBC transfusion burden reduction by ≥ 50% and by ≥ 4 RBC U for ≥ 12 weeks.

Gerds et al. Abstract n. 2992. ASH 2020

Impact of anemia improvement with MMB (JAK2&ALK2i) on survival: MMB data (Simplify 1&2)

Symplify-1 (MMB *vs* RUX)
MMB results at W24

- SVR35: 27%
- TTS50: 28%
- Anemia improvement



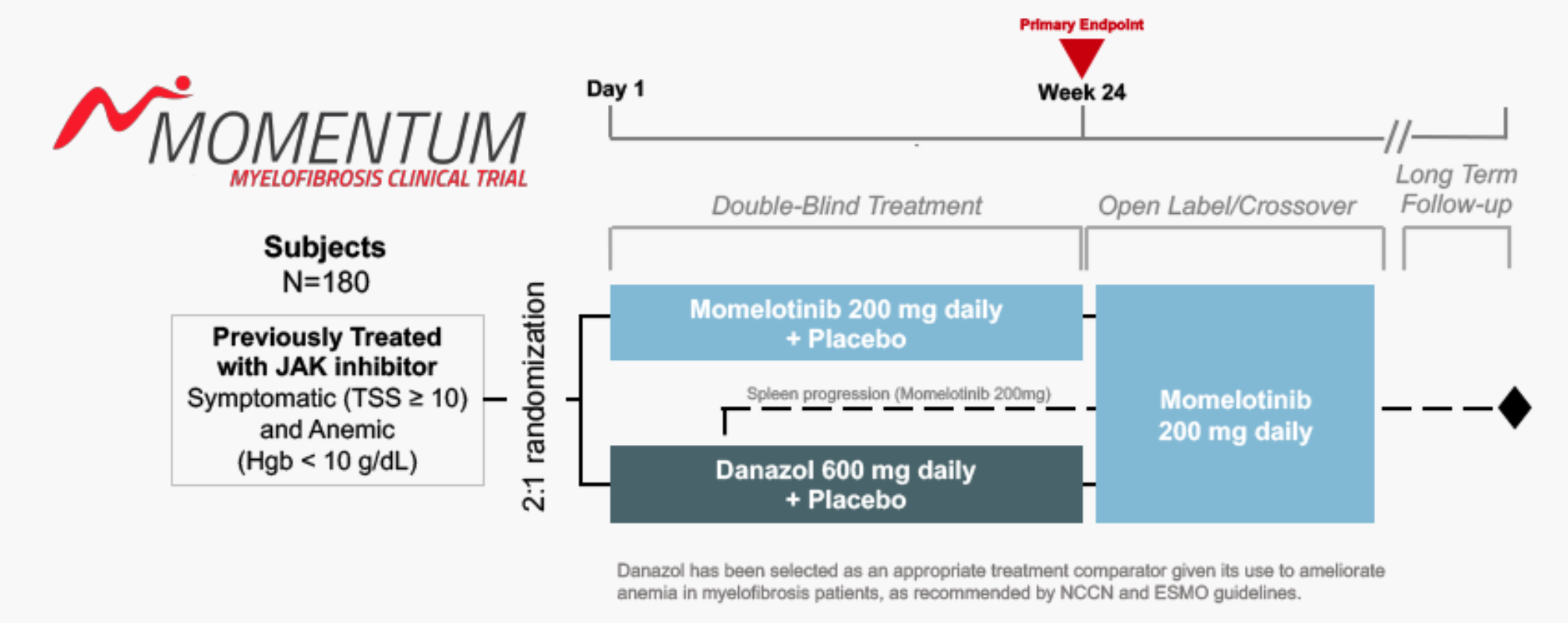
OS data for patients receiving MMB in S1 grouped as W24 transfusion independence (TI) responders vs non-responders

- In S1, W24 TI responders in the MMB group show an OS advantage, with median OS not reached and 3-year survival of 80% (HR = 0.30) compared to MMB TI non-responders
- In S2, W24 TI responders in the MMB group show a trend toward better OS compared to TI non-responders (HR = 0.57)

Mesa et al. EHA 2021. Abst. S202

The phase 3 MOMENTUM study in JAKi-treated patients: MMB vs DAN

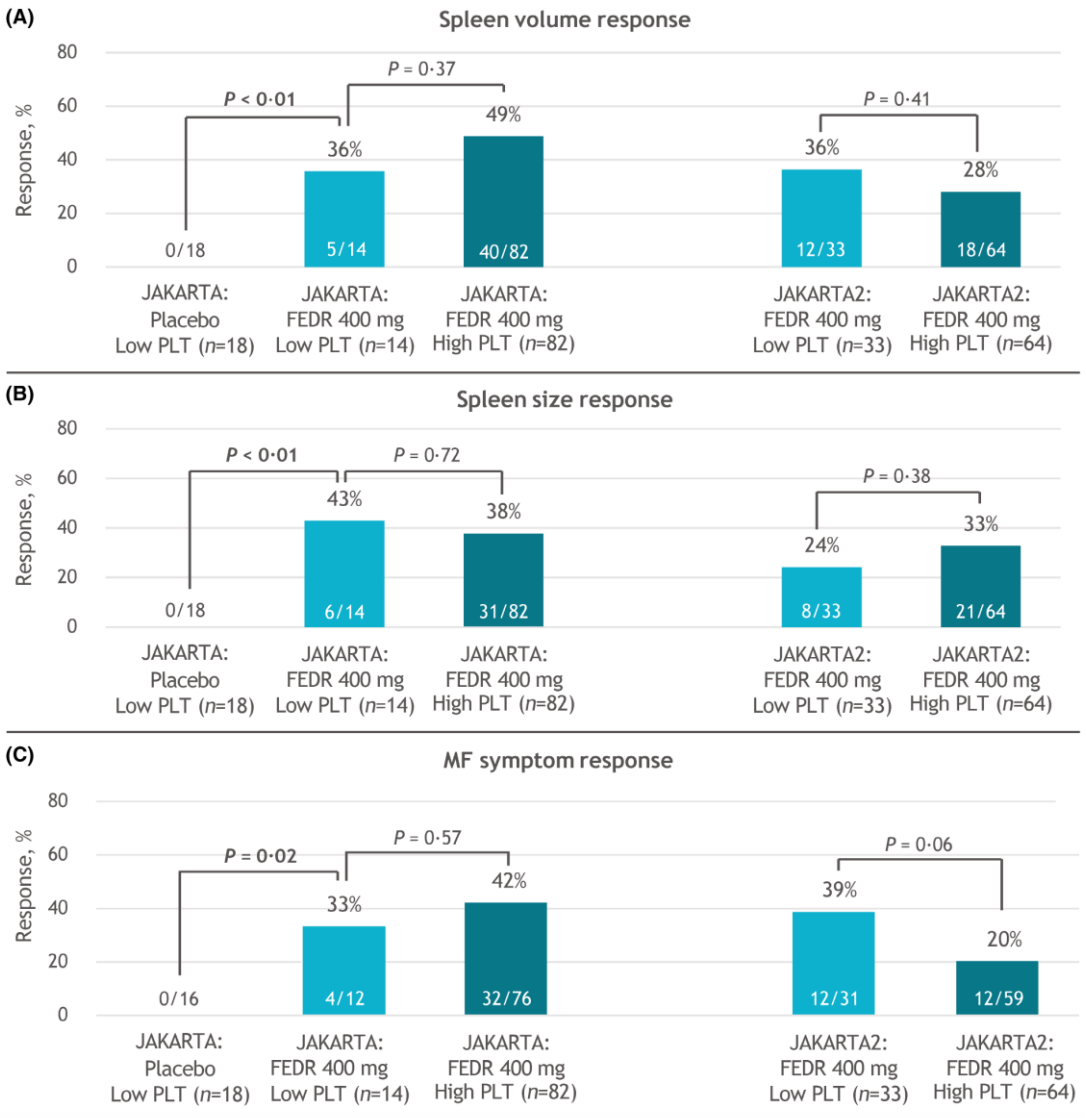
Verstovsek et al. EHA 2022 - 06/11/22; S195



- Primary endpoint: TSS50 at W24
- Secondary endpoints: SVR35, TI status at W24

- Unmet medical need: thrombocytopenia

FED in JAKi-naïve MF with low PLT counts (50-100 x10^9/L)

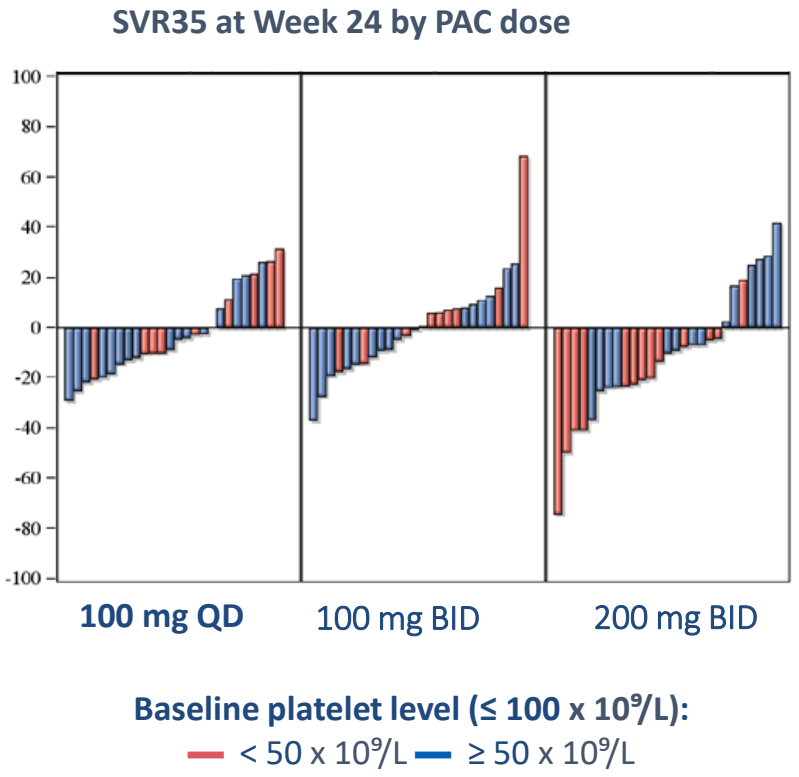


- Overall, in JAKARTA study, at week 24 SVR35 was 47% and symptom response rate was 40% with FED at 400 mg/d
- 14/96 patients (15%) in JAKARTA and 33/97 (34%) in JAKARTA2 had PLT counts 50 to <100 × 10^9/l at enrolment

Harrison et al. Br J Haematol . 2022 Apr 27. Pardanani et al, JAMA Oncol. 2015;1:643-51. Harrison et al, Br J Haematol. 2021 Oct;195(2):244-248.; Pardanani et al, Br J Haematol. 2021

PAC in MF with very low PLT counts (< 50 x10^9/L)

- Patients were randomized 1:1:1 to pacritinib 100 mg QOD, 100 mg BID, or 200 mg BID
- Enhanced eligibility criteria, monitoring, and dose modifications were implemented to mitigate risk of cardiac and hemorrhagic events



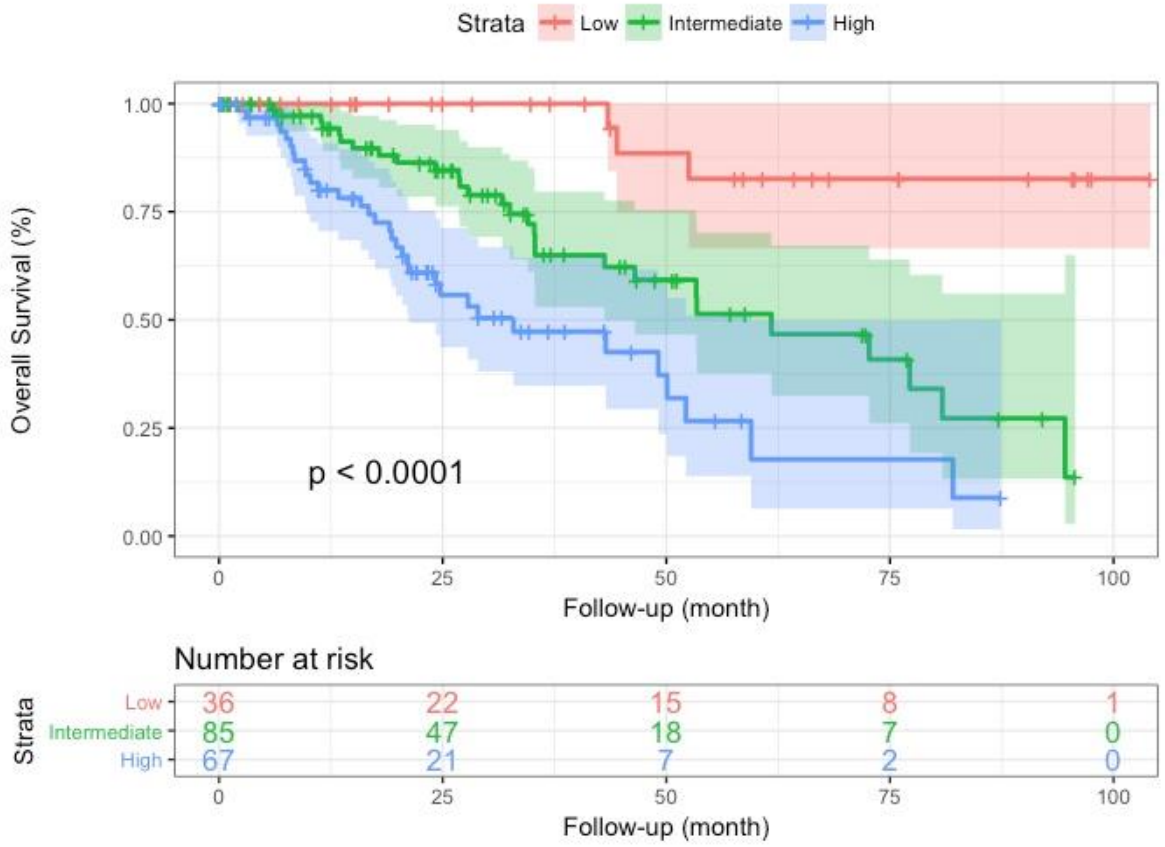
Dose Group	Patients with ≥35% SVR
100 mg QD	0/52 (0%)
100 mg BID	1/55 (1.8%)
200 mg BID	5/54 (9.3%)
PLT < 50 x 10^9/L	4/24 (17%)

- PLT count stability over time, independent from baseline value
- No excess of grade ≥3 hemorrhagic or cardiac events at 200 mg twice per day.

Gerds et al, Blood Adv.2020;4:5825-35

- Unmet medical need: RUX relapse/resistance

Response to RUX after 6 months of treatment impacts on survival in intermediate and high-risk patients: the RR6 model (http://www.rr6.eu)

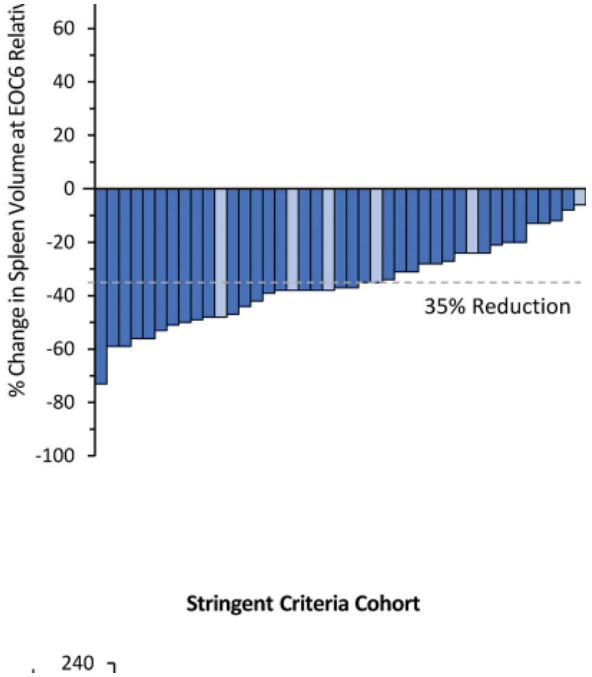


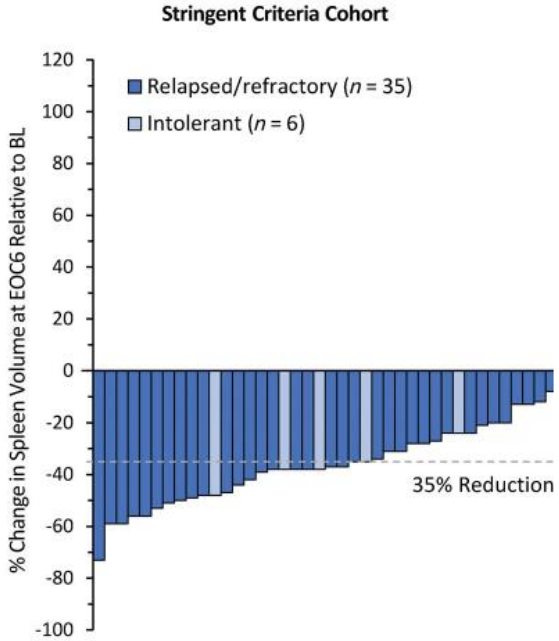
Risk factors	Points
RUX dose <20 mg BID at BL, M3, M6	1
≤30% spleen length reduction at M3 and M6	1.5
RBC transfusions at M3 and/or M6	1
RBC transfusions at BL, M3, and M6	1.5

Risk category	%. of pts	OS	HR	Score
low	19	NR		0
intermediate	45	61	43-80	1-2
high	36	33	21-50	>=2.5

Maffioli M et al. Blood Adv. 2022 Feb 7

Fedratinib in 2nd line, data revisited from the JAKARTA-2 study





- 79 pts with stringent criteria for RUX rel/ref/int; median RUX duration: 10.7 mos
- Data at week 24:
  - SVR35 was 30%
  - Median duration of SVR35 was NR
  - TSS50 was 27%.
  - Grade 3-4 anemia (38%)
  - Grade 3-4 thrombocytopenia (22%)
- SVRRs reached regardless reason for RUX switch, n. of prior therapies, PLT, Hb, age, *JAK2* mutational status

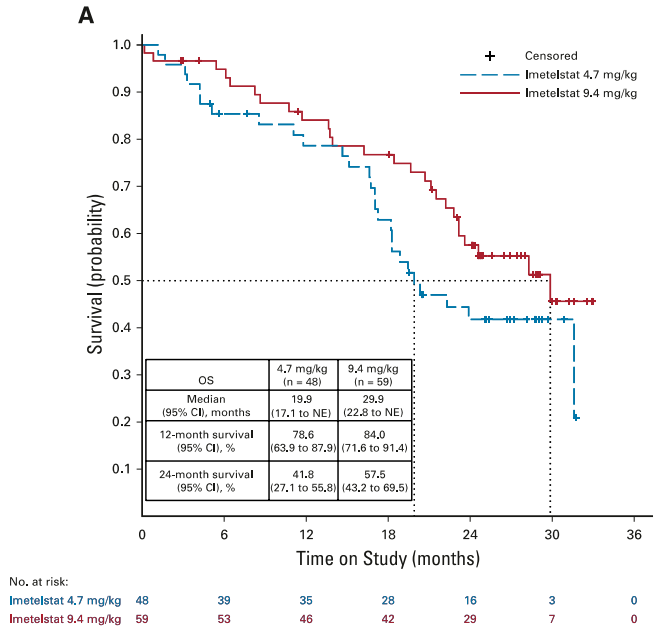
RUX Failure Cohort
Relapse: RUX treatment for ≥ 3 months with regrowth, defined as < 10% SVR or < 30% decrease in spleen size from baseline, after initial response
Refractory: RUX therapy for ≥ 3 months with < 10% SVR or < 30% decrease in spleen size from baseline
Intolerance: RUX treatment for ≥ 28 days complicated by new RBC transfusion need (≥ 2 units per month for 2 months); or grade ≥ 3 thrombocytopenia, anemia, hematoma and/or hemorrhage on RUX

Harrison et al, Lancet Haematol. 2017;4:e317-24. Harrison et al, Am J Hematol. 2020;95:594-603

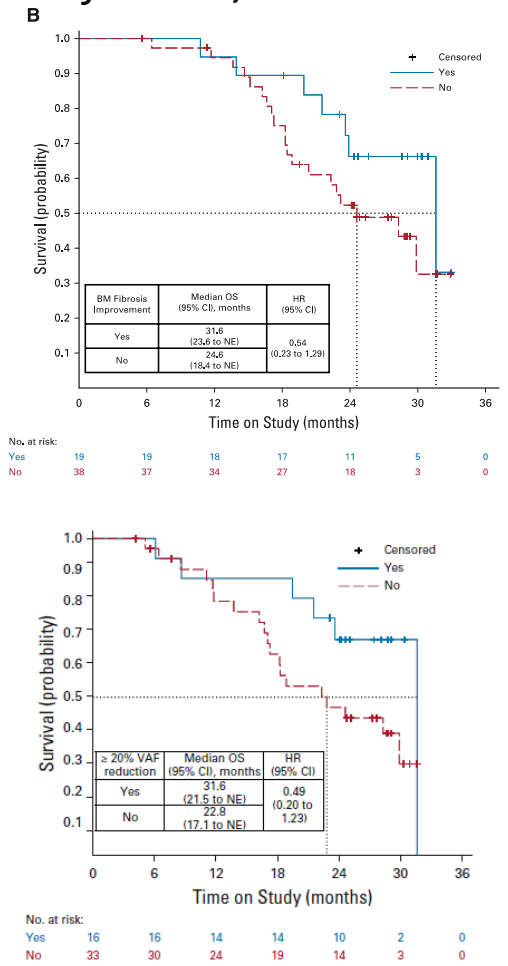
Imetelstat in R/R MF prolong survival at higher dose: IMbark Phase II trial

- RUX-intolerant excluded
- Pts randomized to receive IME 9.4 mg/kg or 4.7 mg/kg IV once every 3W
- Reduction in >1 grade of BMF in 40.5%
- VAF reduction of driver mut. in 42.1%

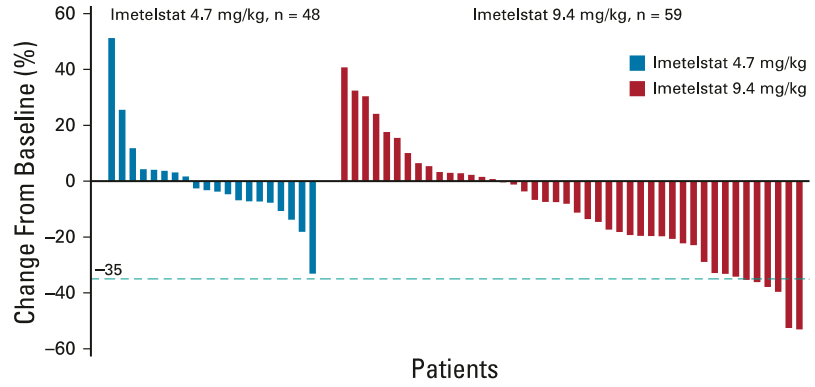
Survival advantage with higher dose



BM fibrosis / JAK2 VAF vs OS



SVR35



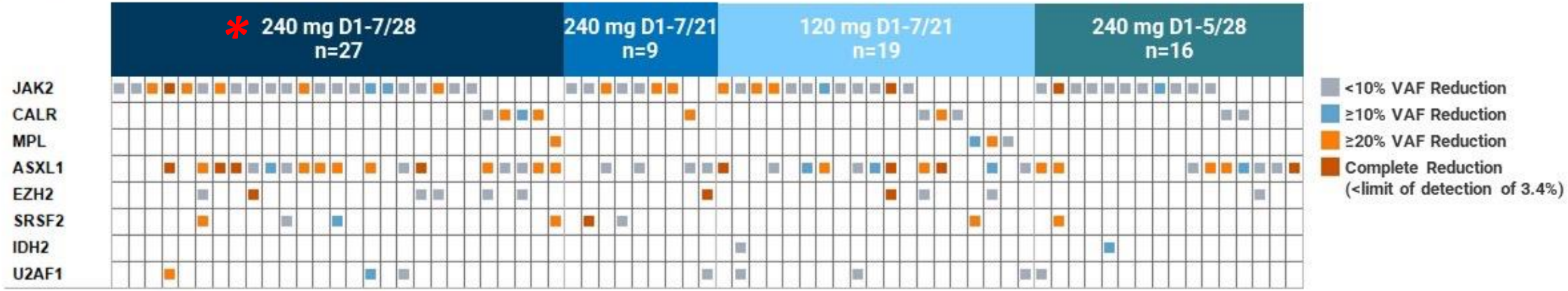
Spleen Response	4.7 mg/kg (n = 48)	9.4 mg/kg (n = 59)
≥ 10% SVR at week 24, No. (%)	4 (8.3)	22 (37.3)
≥ 20% SVR at week 24, No. (%)	1 (2.1)	13 (22)
≥ 35% SVR at week 24, No. (%)	0	6 (10.2)

Mascarenhas et al. Clin Oncol 2021 Sep 10;39(26):2881-2892

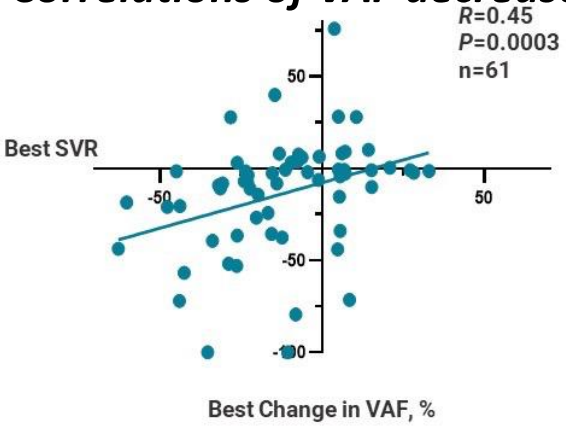
Early effect of Navtemadlin (KRT-232) monotherapy (KRT-232-101) in 113 JAKi relapsed/refractory MF

- Int/HR DIPSS, Tp53 wtHMR mut in 58%
- W24-SVR35 in 16%

Best decrease of VAF of mutated genes

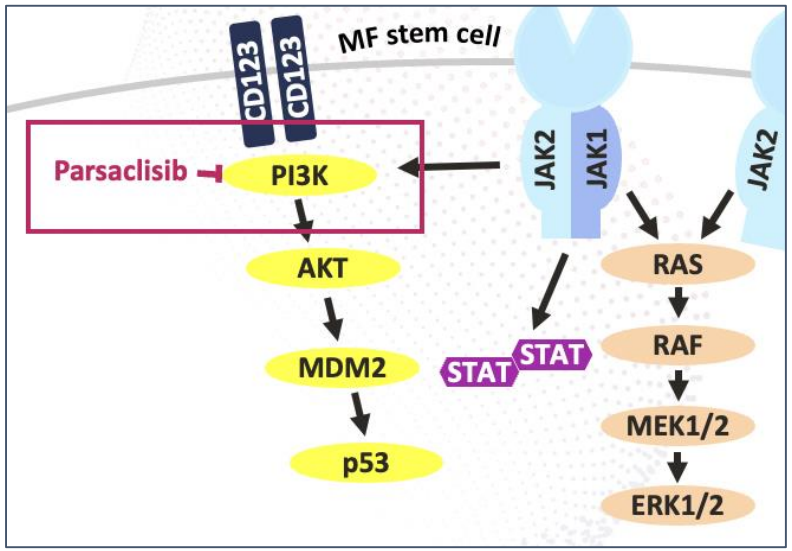


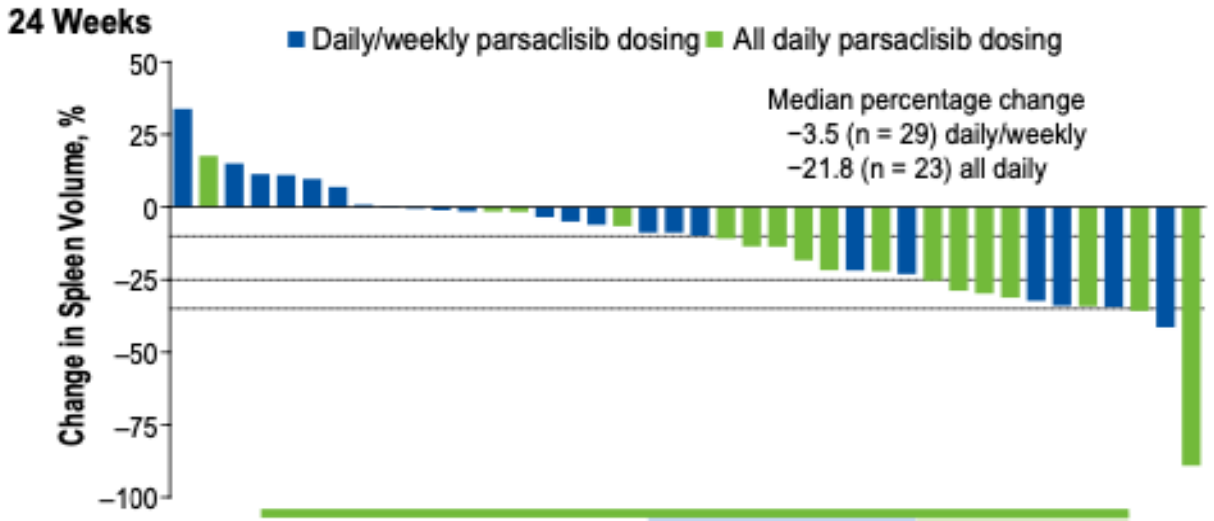
Correlations of VAF decreased and SVR35



Vachhani et al . ASH 2021

Parsaclisib+RUX in MF with RUX suboptimal response





Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 24	n = 29	n = 23
≥10% reduction	6 (21)	13 (57)
≥25% reduction	4 (14)	7 (30)
≥35% reduction	1 (3)	2 (9)

All daily dosing group:

- TSS50 at W24: 19%
- Hb levels steady over the study
- No G≥2 diarrhea or rash
- 29% ≥G3 thrombocytopenia

Figure adapted from: Tremblay & Mascarenhas, Cells. 2021;10:1034. Yacoub et al, Abstract EP1075, EHA 2021

Early effect of navitoclax+RUX in 34 pts with RUX suboptiomal responses (REFINE Study)

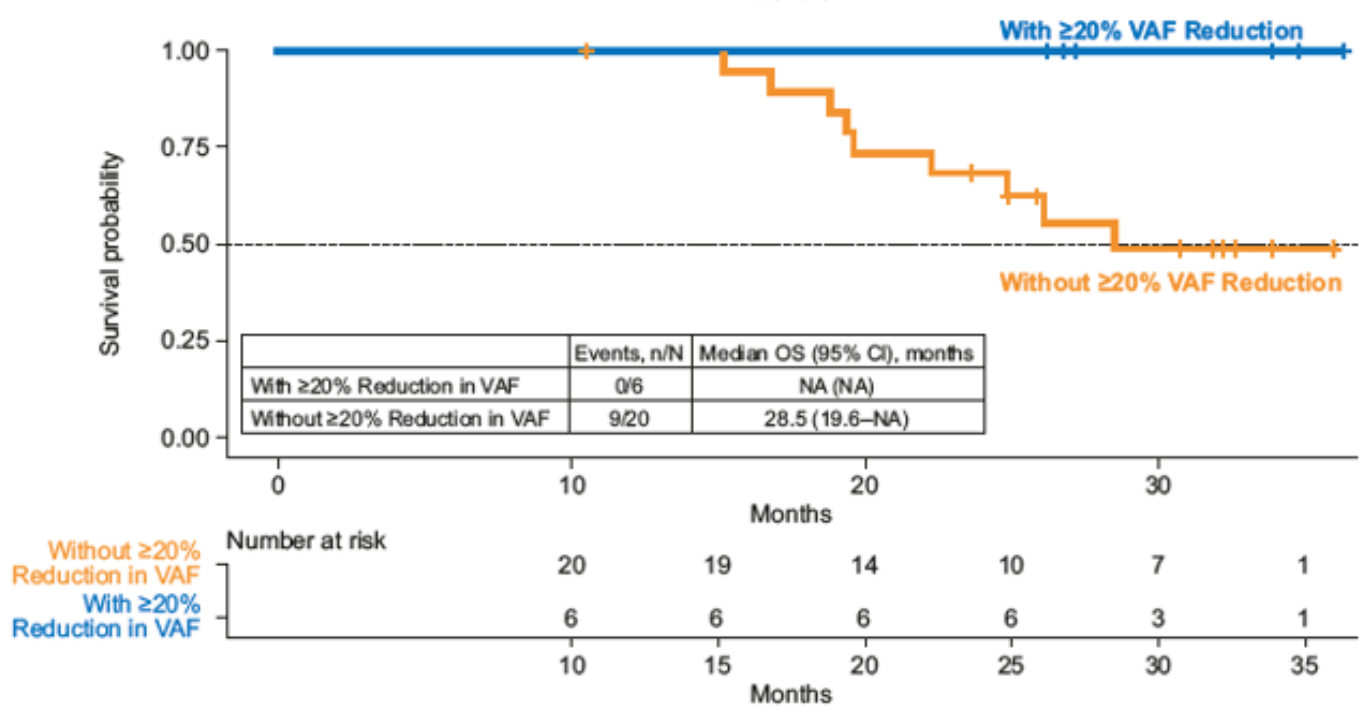
- 31% of patients had SVR_{35} at week 24 in the HMR group, as did 31% of the non-HMR group
- In 33%, BM fibrosis improved >= 1 grade at any time on study: 21% at W24
- 39% in the HMR group had an improvement in fibrosis >=1 grade *vs.* 36% of non-HMR group
- In 46%, *JAK2/CALR* VAF reduced >10%
- 28% had reductions in VAF >=20% in the HMR group vs. 17% in the non-HMR group

- Int/HR DIPSS, HMR mut in 58%. NAV at 100mg/200 mg per PLT count
- W24-SVR35 in 26.5%; anytime 41%; median duration 14 m
- Mean Hb level stable
- Among 11 pts with Hb <10 g/dL at BL 64% increased Hb > 2 g/dL; ½ TD become TI

Harrison et al, J Clin Oncol . 2022 Feb 18; Pemmaraju et al. Lancet Haematol. 2022 May 13

The improvements in VAF in patients with MF treated with Navitoclax+ Ruxolitinib is associated with improved OS

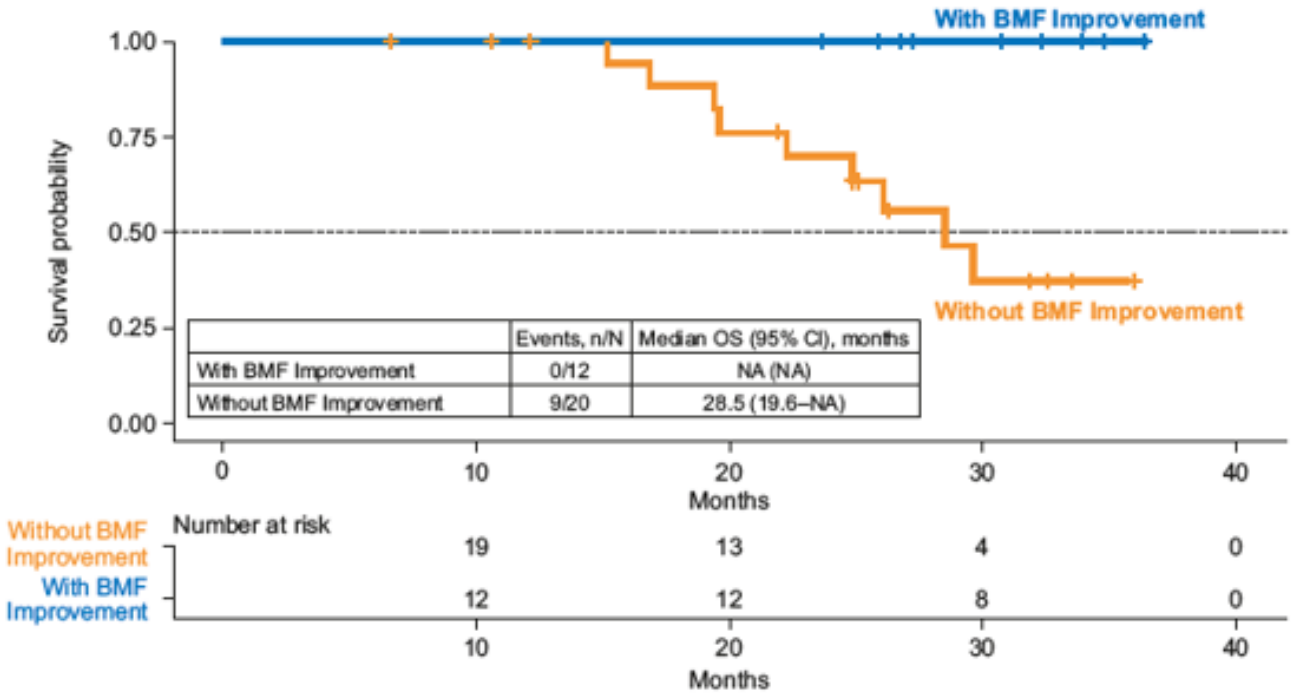
- 6 out of 26 patients who received ≥1 dose of navitoclax plus ruxolitinib and were evaluable for molecular risk achieved ≥20% VAF reduction at week 24
- Median OS was not reached for patients with ≥20% VAF reduction vs 28.5 months for those with <20% reduction (n=20; 95% CI, 19.6-NE; *P*=0.05)



Pemmaraju et al. Lancet Haematol. 2022 May 13

The improvements in BM fibrosis in patients with MF treated with Navitoclax+ Ruxolitinib is associated with improved OS

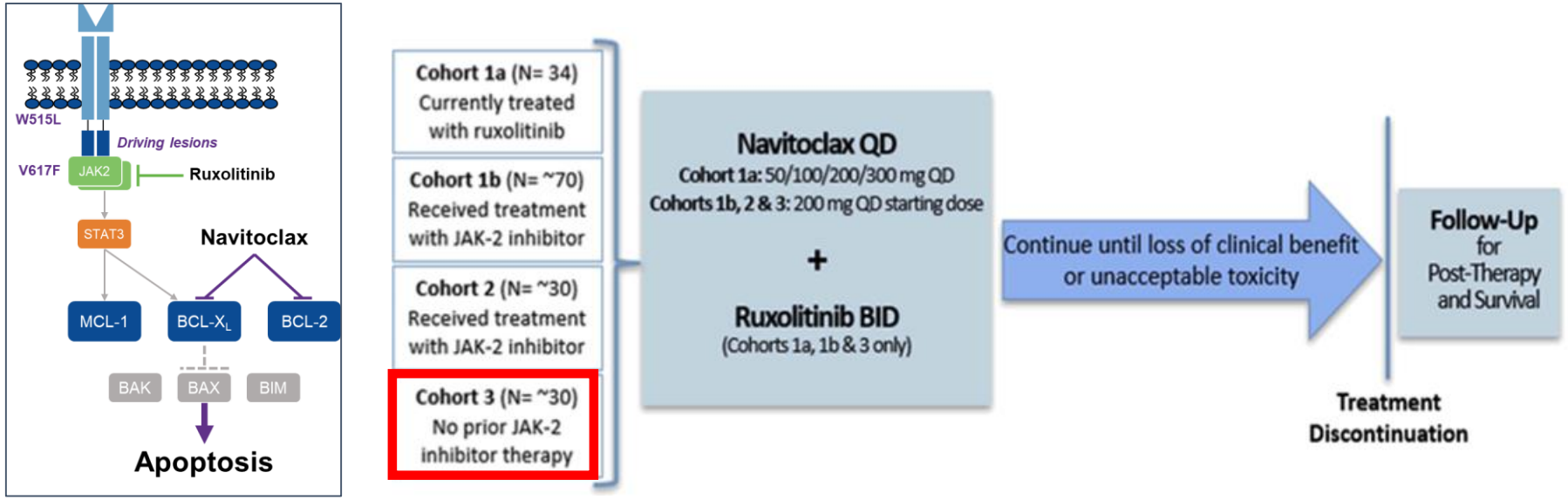
- 12 out of 32 patients who received ≥1 dose of navitoclax plus ruxolitinib and were evaluable for BMF achieved ≥1 grade improvement on study
- Median OS was not reached for patients with ≥1 grade improvement in BMF *vs.* 28.5 months for those without BMF improvement



Pemmaraju et al. Lancet Haematol. 2022 May 13

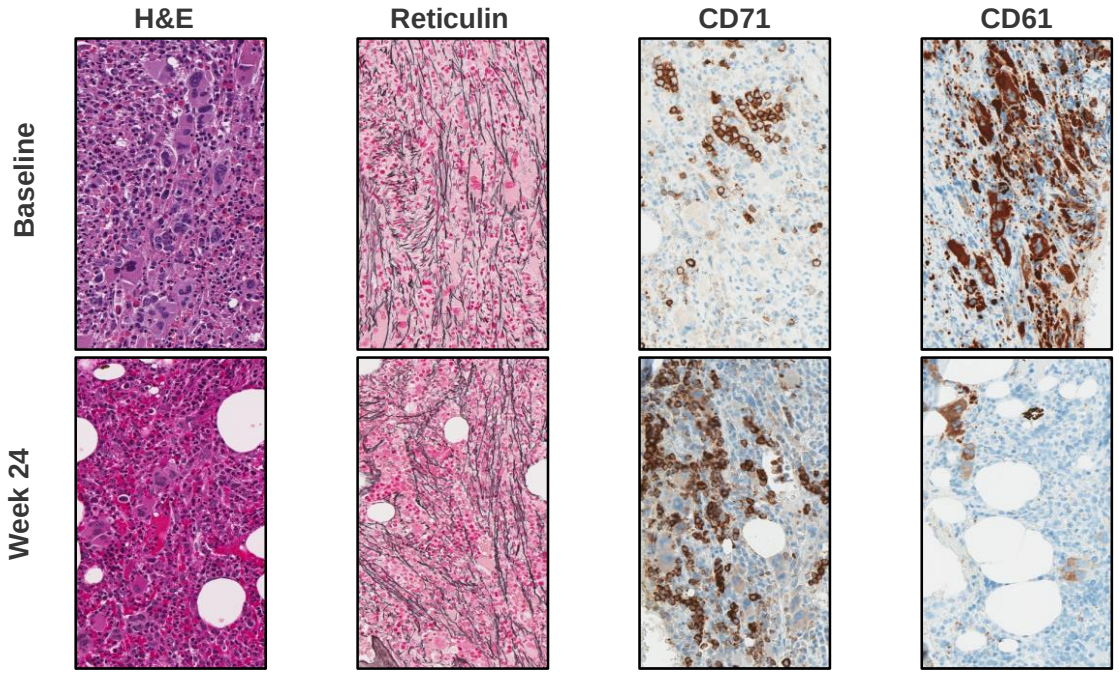
NAVITOCLAX PLUS RUXOLITINIB IN JAK INHIBITOR-NAÏVE PATIENTS WITH MYELOFIBROSIS: PRELIMINARY SAFETY AND EFFICACY IN A MULTICENTER, OPEN-LABEL PHASE 2 STUDY

Passamonti *et al*. EHA 2022 - 06/11/22; S197

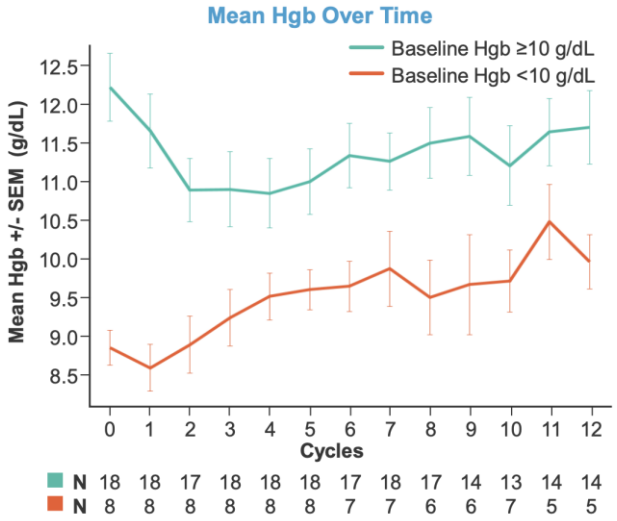


Early effects of pelabresib+RUX in 78 RUX-naive MF patients (arm 3, MANIFEST study)

- 33% (16/48) had at least 1G improvement in BMF
- 88% (14/16) of improvements occurred within 6 mos



- Int/HR DIPSS, HMR mut in 55%
- Pela 125 mg/d 14/28
- W24 SVR35 68%; anytime: 86%. 86% maintained SVR35



Verstovsek et al. ASH 2021 Abs 2568; Mascarenhas et al, ASH 2020, Abs 55; Kremyanskaya et al, EHA 2021, Abs EP1085

Summary and conclusions

- Ruxolitinib is the standard treatment for MF
- Fedratinib is FDA/EMA-approved for MF as first line and after ruxolitinib failure
- Pacritinib is FDA-approved for MF patients with very low PLT counts; momelotinib approval is under way
- Other targeted therapies are under investigation with the potential to be disease-modifying