Beyond JAK inhibitors in MF

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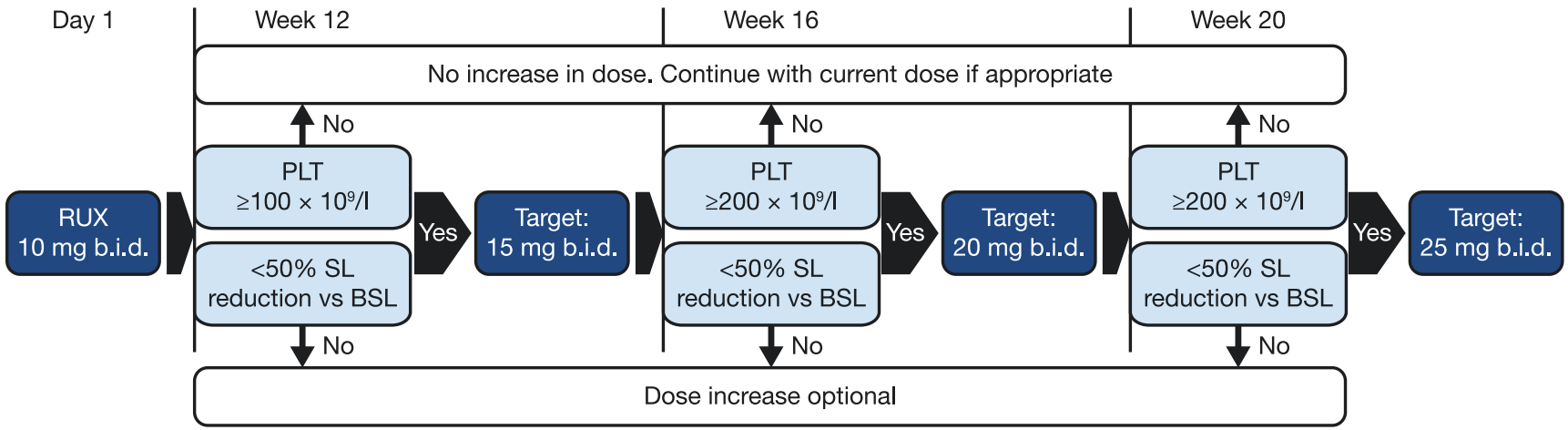
- Unmet medical need: anemia

RUX in MF with anemia (the Realise trial)

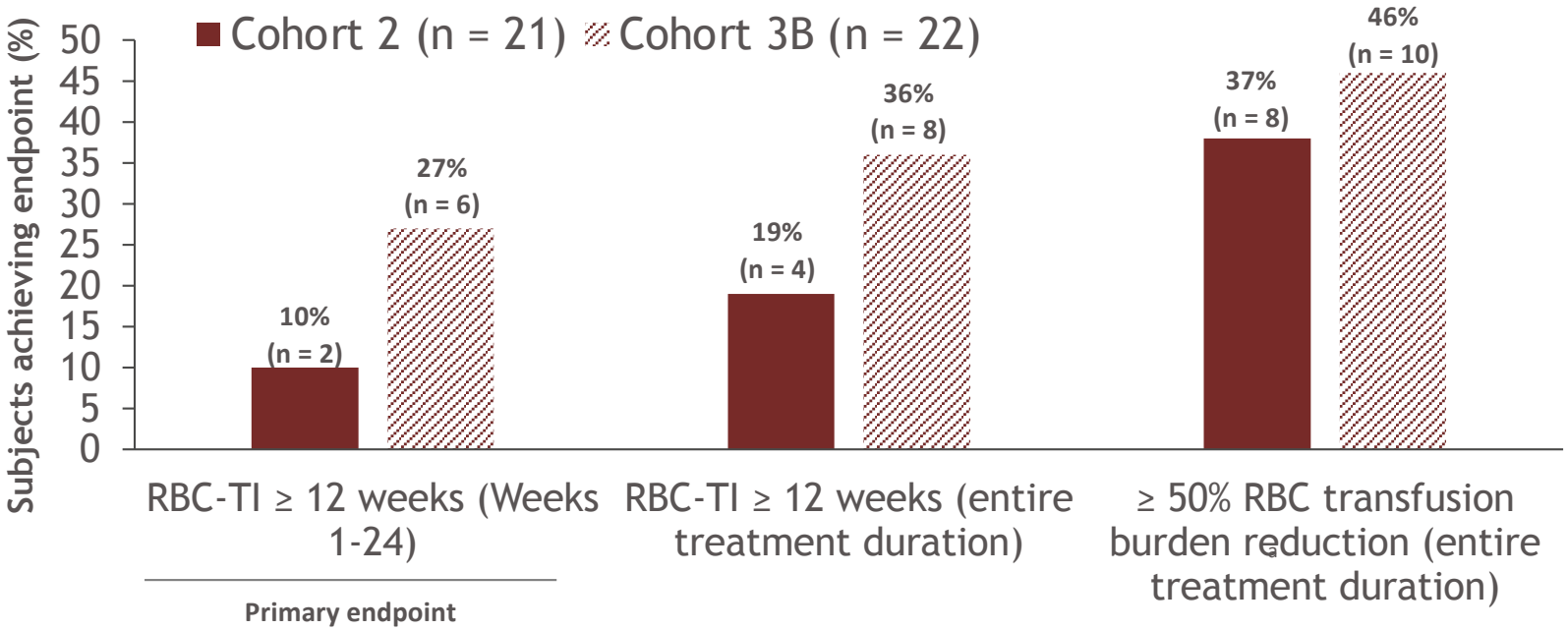


- Int-1, 17%
- >50% reduction in spleen length by week 24: 56%
- 55% of Int-1, 57% of Int-2 and 40% of HR patients achieved a >50% reduction in SL by week 24.
- A total of 70% of patients achieved a >50% reduction in SL at any time during the study

Cervantes et al. Leukemia 2021

Luspatercept on the top of RUX in TD MF to improve anemia

- **Rates of RBC-TI and ≥ 50% transfusion burden reduction ≥ 12 weeks**

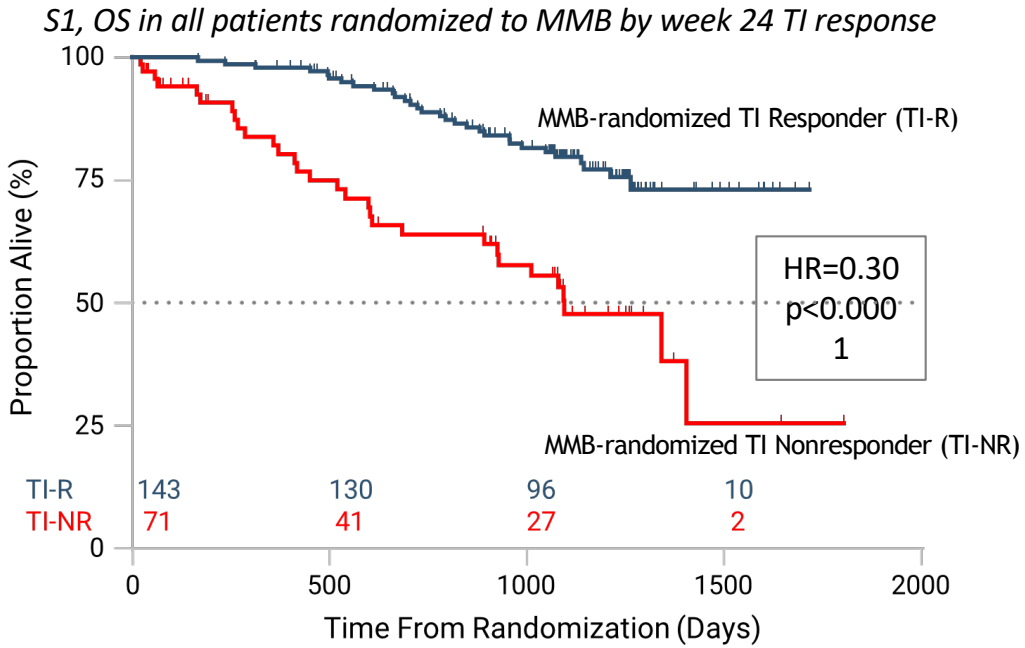


[a]Defined as RBC transfusion burden reduction by ≥ 50% and by ≥ 4 RBC U for ≥ 12 weeks.

Gerds et al. Abstract n. 2992. ASH 2020

Momelotinib, a JAK inhibitor, can improve anemia, eventually resulting in improved survival (Symplify 1&2)

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



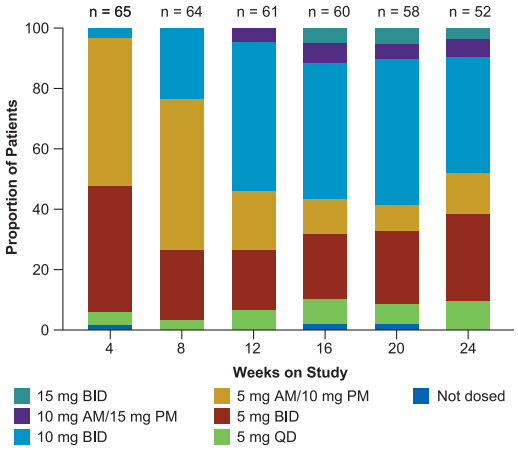
- In S1, W24 TI responders in the MMB group show an OS advantage, with median OS not reached and 3-year survival of 80% (HR = 0.30) compared to MMB TI non-responders
- In S2, W24 TI responders in the MMB group show a trend toward better OS compared to TI non-responders (HR = 0.57)

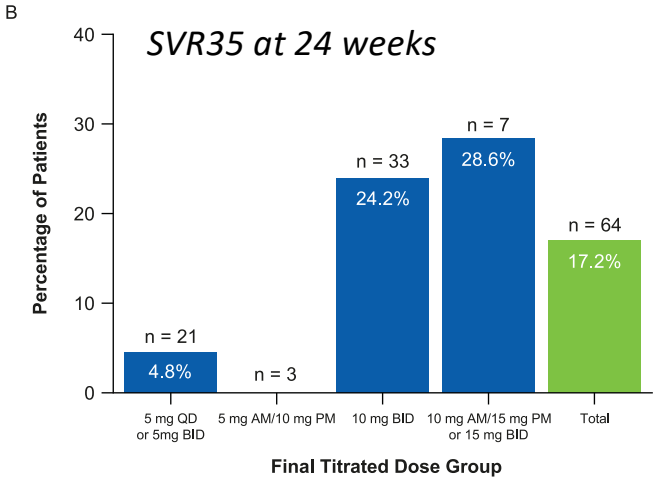
Mesa et al. EHA 2021. Abst. S202

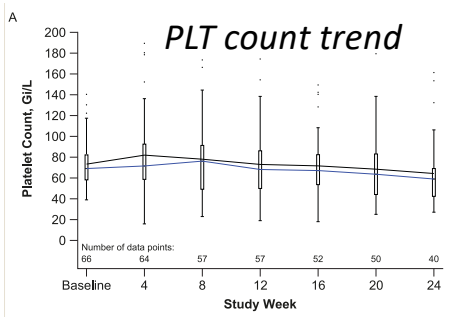
- Unmet medical need: thrombocytopenia

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

- RUX was initiated at 5 mg BID with gradual up-titration based on response and hematologic parameters





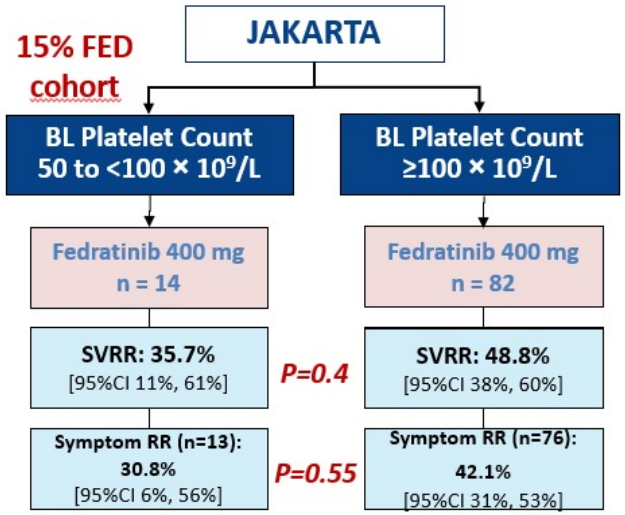


Talpaz et al. Clinical Lymphoma, Myeloma and Leukemia, 2021

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

Clinical trial and numerosity	Trial-specific features and results
JAKARTA **FED *vs* Placebo**	Phase 3 JAKi naïve
FED 400 mg QD (n = 96) **FED 500 mg QD (n = 97)** **Placebo (PBO, n = 96)**	*Fedratinib 400 mg QD* **SVR35 W24:** 37% **TSS50 W24**: 40% ≥G3 anemia: 34%

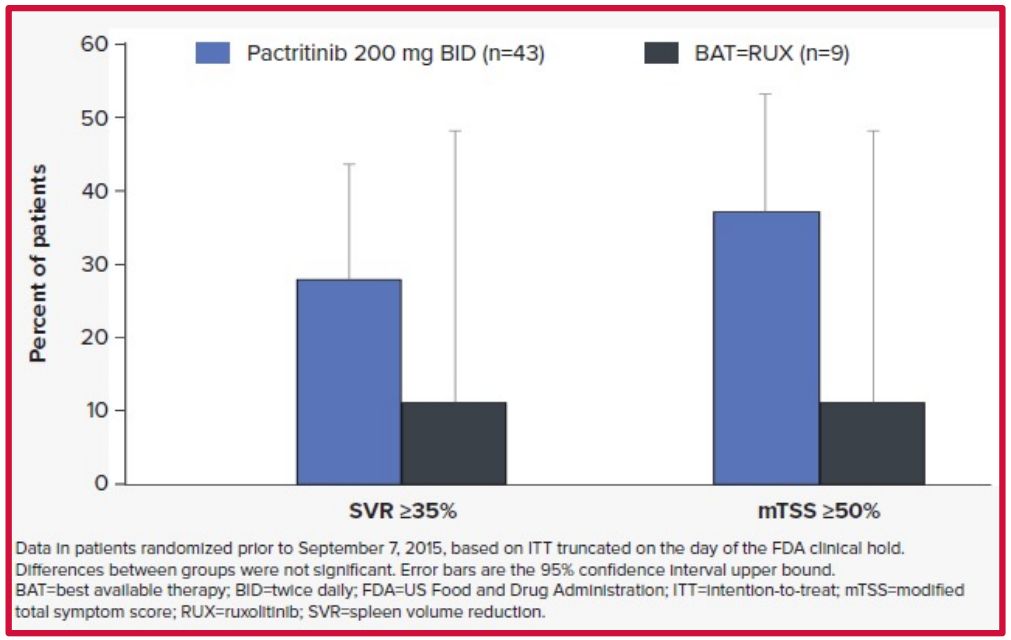
Overall, at week 24, SVR35 was 47% and symptom response rate was 40% with fedratinib 400 mg



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*

Pacritinib vs. RUX in MF with low PLT counts (< 100 x10^9/L)

- Analysis on RUX-naive patients of the PERSIST-2, PAC at 200 mg BID dosage
- PAC (42), vs. RUX (9)
- Patients treated with pacritinib had numerically higher rates of SVR (28% vs 11%) and mTSS response (37% vs 11%) compared with patients treated with ruxolitinib.

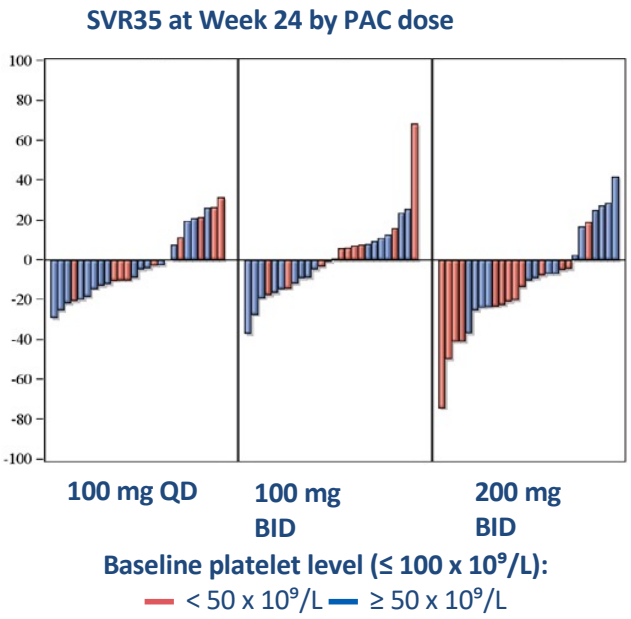


Data in patients randomized prior to September 7, 2015, based on ITT truncated on the day of the FDA clinical hold.
Differences between groups were not significant. Error bars are the 95% confidence interval upper bound.
BAT=best available therapy; BID=twice daily; FDA=US Food and Drug Administration; ITT=intention-to-treat; mTSS=modified total symptom score; RUX=ruxolitinib; SVR=spleen volume reduction.

Mascarenhas et a. ASH 2021, abstr 3639

Pacritinib 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



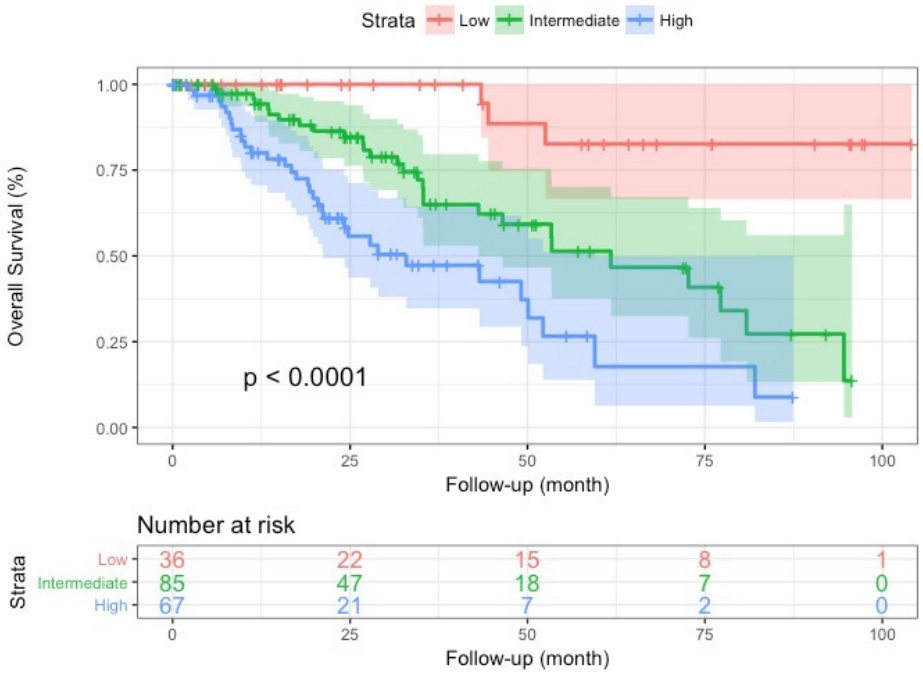
Dose Group	Patients with ≥35% SVR
100 mg QD	0/52 (0%)
100 mg BID	1/55 (1.8%)
200 mg BID	5/54 (9.3%)
PLT < 50 x 10^9/L	4/24 (17%)

- 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 MF: the RR6 model



Negative parameters	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

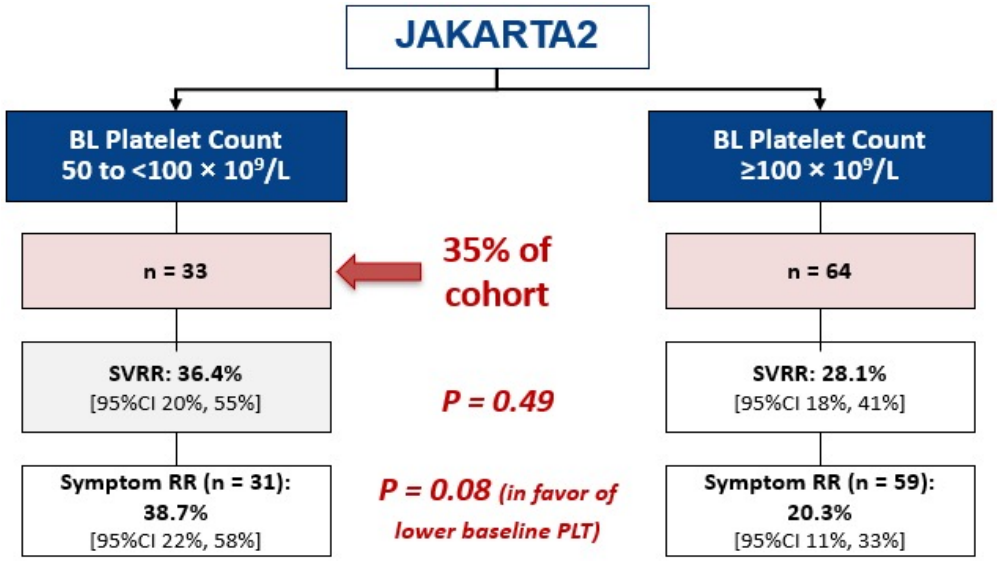
Risk category	%. of pts	OS	HR	Score
Low	19	NR		0
Intermediate	45	61	43-80	1-2
High	36	33	21-50	>=2.5

Maffioli M et al. Blood Adv. 2022 Feb 7

Fedratinib in RUX failure: the JAKARTA-2 trial

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

FED 400 mg QD (n = 97)	% of Patients
SVR35 W24	31%
TSS50 W24	27%
G≥3 anemia	38%
G≥3 thrombocytopenia	22%



FED is equally active in case of low baseline PLT count

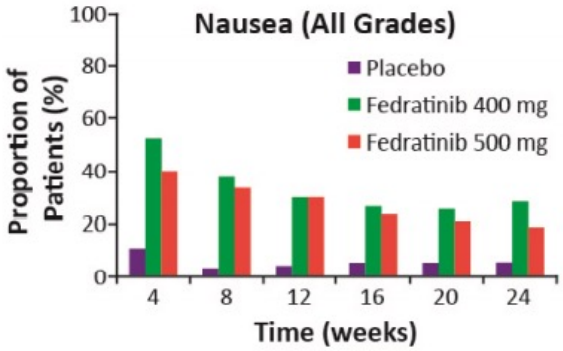
Harrison et al, Lancet Haematol. 2017;4:e317-24. Harrison et al, Am J Hematol. 2020;95:594-603

FED: management of gastrointestinal (GI) events

JAKARTA trials

- No measures to prevent GI toxicity
- 40-60% patients: low grades nausea, vomiting, diarrhea

JAKARTA

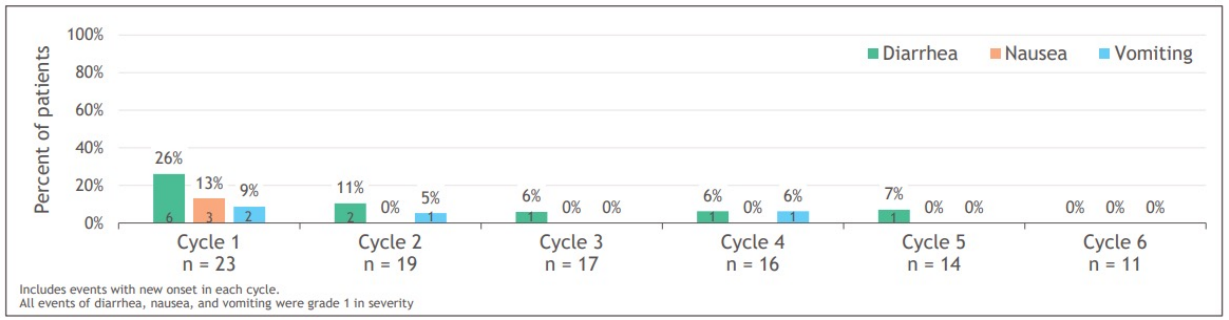


FREEDOM trials

Required mitigation strategies:

- drugs for prophylactic and symptomatic use
- FED administration with food and dosing modifications

FREEDOM

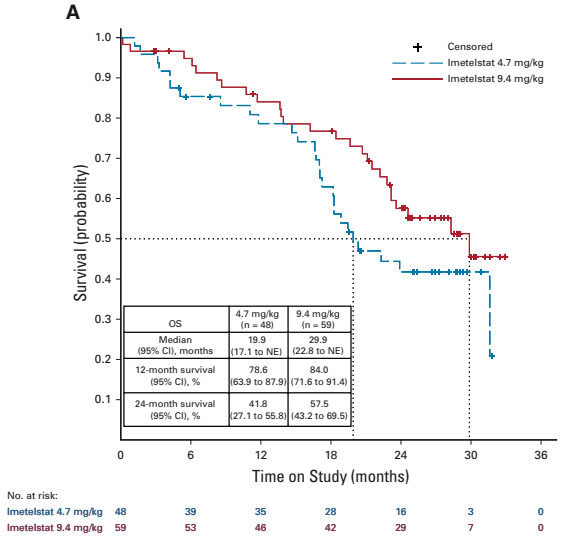


Pardanani et al, JAMA Oncol. 2015;1:643-51. Harrison et al, Lancet Haematol. 2017;4:e317-24. Gupta et al, Abstract MPN-183, SOHO 2020

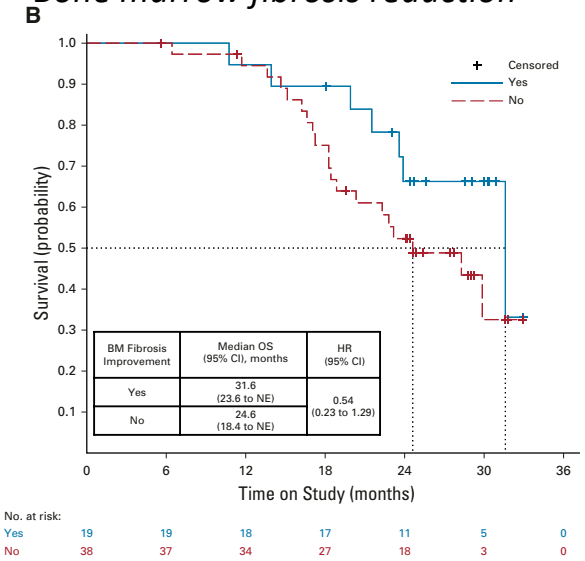
Imetelstat in R/R MF prolong survival at higher dose: IMbark Phase II trial

- 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%

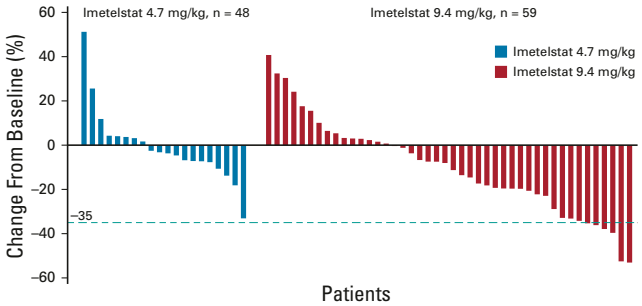
Survival advantage with higher dose



Bone marrow fibrosis reduction



SVR35



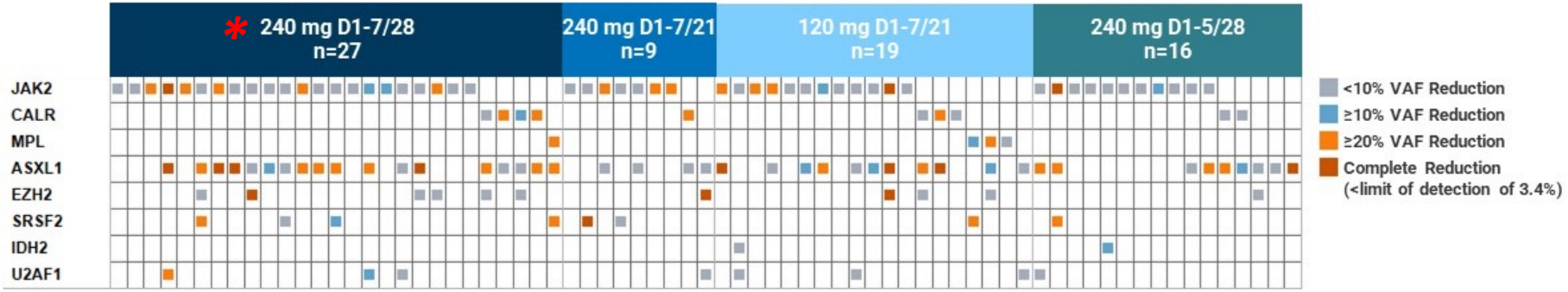
Spleen Response	4.7 mg/kg (n = 48)	9.4 mg/kg (n = 59)
≥ 10% SVR at week 24, No. (%)	4 (8.3)	22 (37.3)
≥ 20% SVR at week 24, No. (%)	1 (2.1)	13 (22)
≥ 35% SVR at week 24, No. (%)	0	6 (10.2)

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

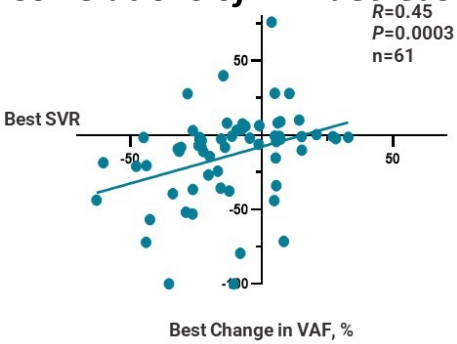
Early effect of Navtemadlin (KRT-232) monotherapy (P2, BOREAS trial) in 113 JAKi relapsed/refractory MF

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

Best decrease of VAF of mutated genes

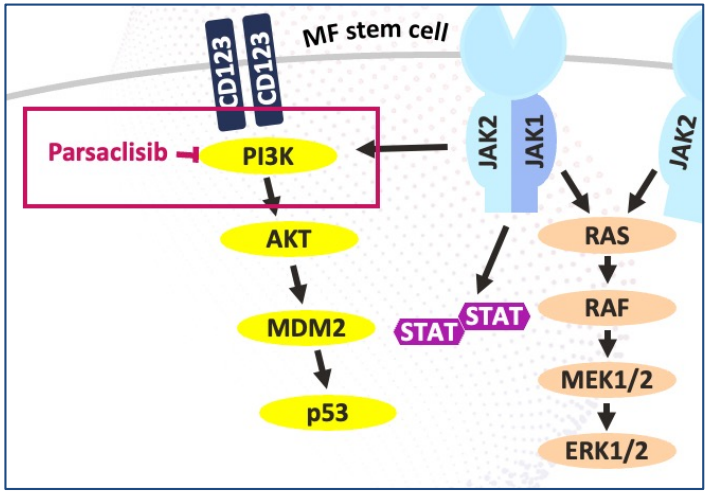


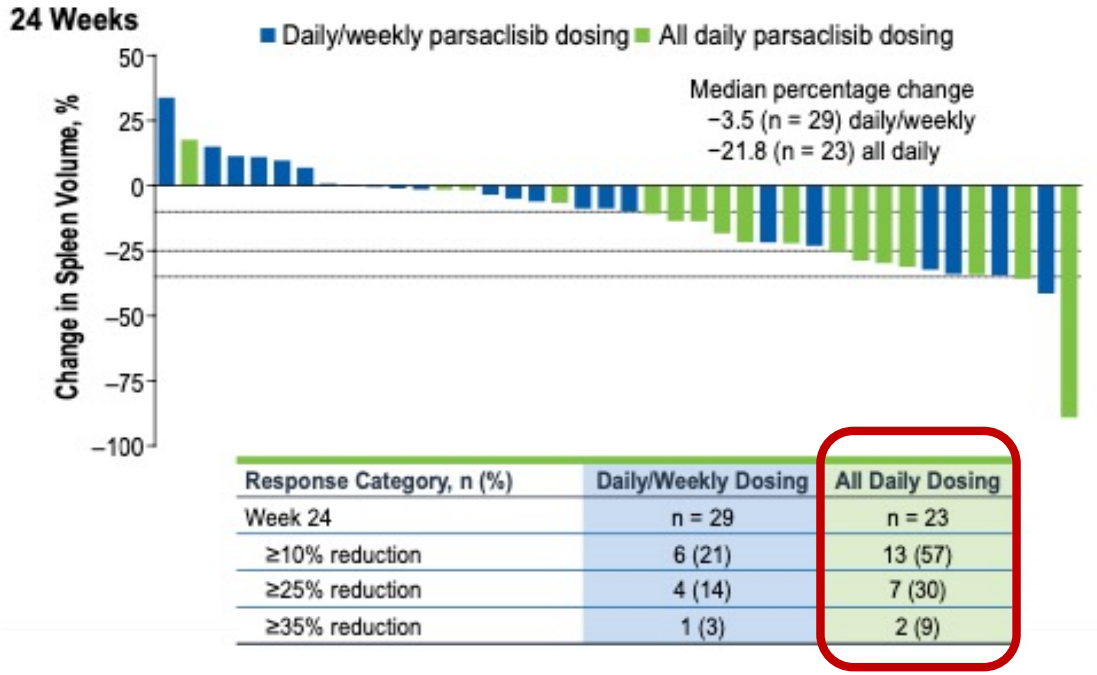
Correlations of VAF decreased and SVR35



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:

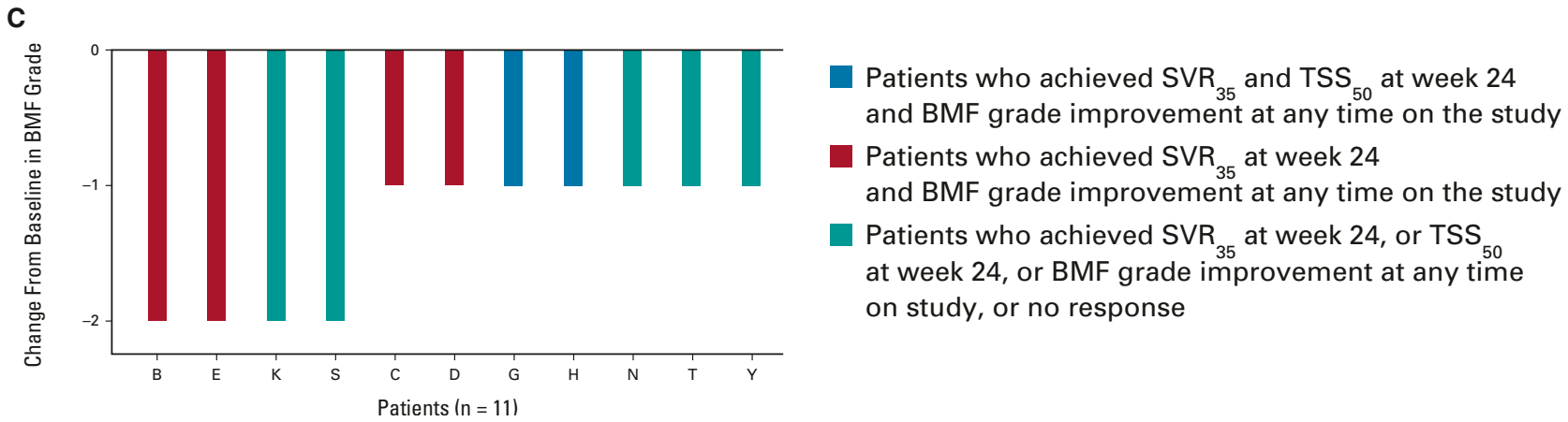
- TSS50 at W24: 19%
- Hb levels steady over the study
- No G≥2 diarrhea or rash
- 29% ≥G3 thrombocytopenia

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

Early effect of RUX plus navitoclax (REFINE Study) on 34 pts with RUX suboptiomal responses

- Int/HR DIPSS, HMR mut in 58%
- W24-SVR35 in 26.5%; anytime 41%; median duration 14 m
- Mean Hb level stable over 30 mos
- Among 11 pts with Hb <10 g/dL at BL 64% increased Hb > 2 g/dL; ½ TD become TI

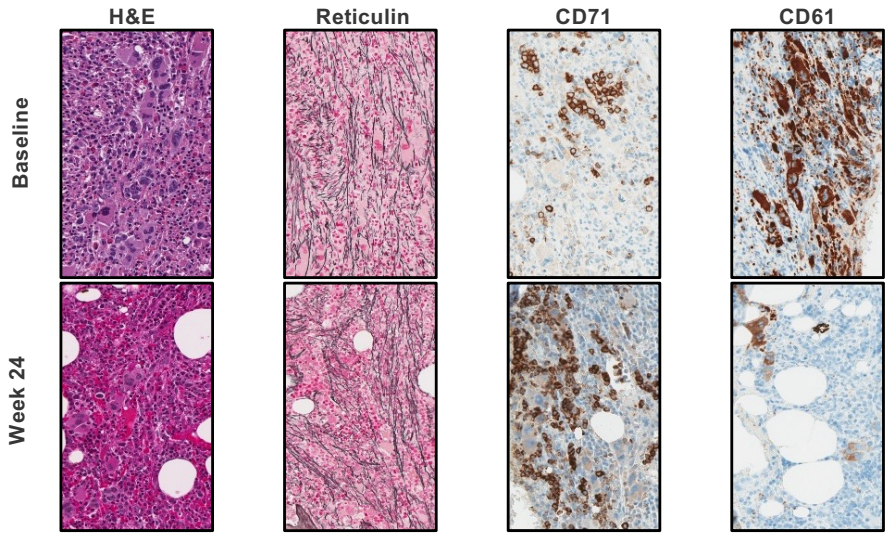
- In 11/33 (33%) pts, BMF improved from baseline by >= 1 grade at any time on study: 1 pt (3%) at W12, 7 (21%) at W24, 2 (6%) at W48, and 1 (3%) at W96
- In 12/26 (46%) pts, *JAK2/CALR* VAF reduced >10%
- Reduction of MF-associated cytokines correlated with SVR



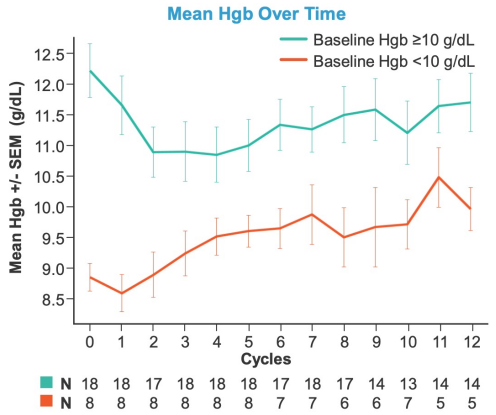
Harrison et al, J Clin Oncol . 2022 Feb 18;JCO2102188.

Early effects of RUX plus pelabresib (arm 3, MANIFEST study) in 78 RUX-naive pts

- 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%
- 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

Proposed definition of disease-modifying activity

- Disease modification in MF is defined as therapy that exerts a clinically meaningful impact on survival out- comes and/or restoration of normal hematopoiesis in conjunction with improvement in bone marrow fibrosis through a substantial and durable reduction in the clonal burden of disease.

Naveen Pemmaraju, Srdan Verstovsek, Ruben Mesa, Vikas Gupta, Jacqueline Garcia, Joseph Scandura, Stephen Oh, Francesco Passamonti, Konstanze Döhner, Adam J Mead. Cancer May 2, 2022

Conclusions

- FED (FDA/EMA approved) reduces SVR and TSS in 30% of patients in 2nd line and it is effective in any line if PLT 50-100 x 10^9/L at baseline
- MMB and PAC could be useful for patients with cytopenias
- Pelabresib, navitoclax, navtemadlin alone or in RUX-based combo are promising and potentially disease modifying
- Results of ongoing phase 3 RCT are largely awaited, to assess the advantages of innovative therapies
- First-line pelabresib + RUX reaches SVR35 in 67% comparing favourably to other single-agent options (30-40% RUX, 27% MMB and 37% FED)
- First-line navitoclax RUX … wait ASCO/EHA 2022