LEUKEMIA2020-2021

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ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

Balancingy toxicity and efficacy of JAK2 inhibitors

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GITMO

SIES Società Italiana Ematologia Sperimentale

SIE - Società Italiana di Ematologia

Ruxolitinib: long term clinical data (5 years)

COMFORT trials are randomized trials with RUX *vs.* placebo or *vs.* best available therapy with a planned cross over and with spleen control as a primary endpoint

- 53% of RUX achieves spleen response at any time
- The probability of maintaining a spleen response was 0.51 at 3 years and 0.48 at 5.0 years

- **Anemia, thrombocytopenia and infections are the key AEs**
- Baseline anemia does not impact on responses
- Development of anemia does not affect survival

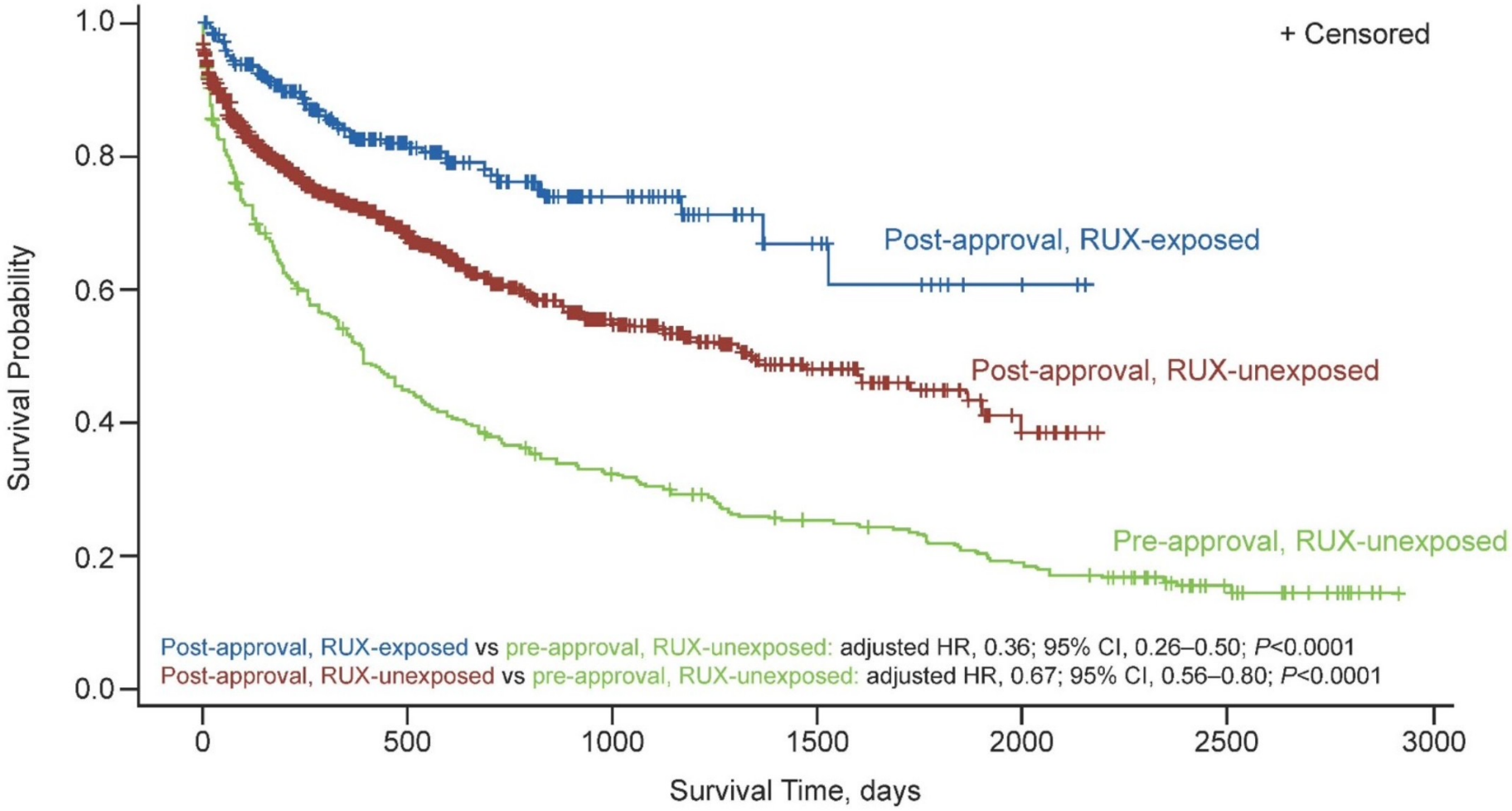
Verstovsek S, et al. Br J Haematol. 2013; 161(4): 508-516; Verstovsek S, et al. N Engl J Med. 2012;366(3):799-807; Gupta V Haematologica. 2016 Dec;101(12):e482-e484.; Verstovsek S, et al. N Engl J Med. 2012;366(3):799-807; Harrison et al; Leukemia. 2016 May 23; Giraldo P, et al. EHA 2015, P675

Data from the Medicare Fee-for-Service claims database on 1677 MF cases

- 278 pts with dx pre-RUX approval (all RUX-unexposed) and 1399 post-RUX approval (RUX-unexposed, n=1127; RUX-exposed, n=272)
- Median follow-up was around 12 months
- The 1-year survival rate (95% CI) was:
  - 55.6% (49.4%–61.3%) for the pre-RUX approval group
  - 72.5% (69.5%–75.2%) for the post-RUX approval RUX-unexposed group
  - 82.3% (76.7%–86.7%) for the post-RUX approval RUX-exposed group
- The risk of mortality was lowest among RUX-exposed patients (adjusted hazard ratio [HR], 0.36; 95% CI, 0.26–0.50; $P<0.0001$ vs the pre-RUX approval group).

Verstovsek et al, ASH meeting 2020 abstract 3089

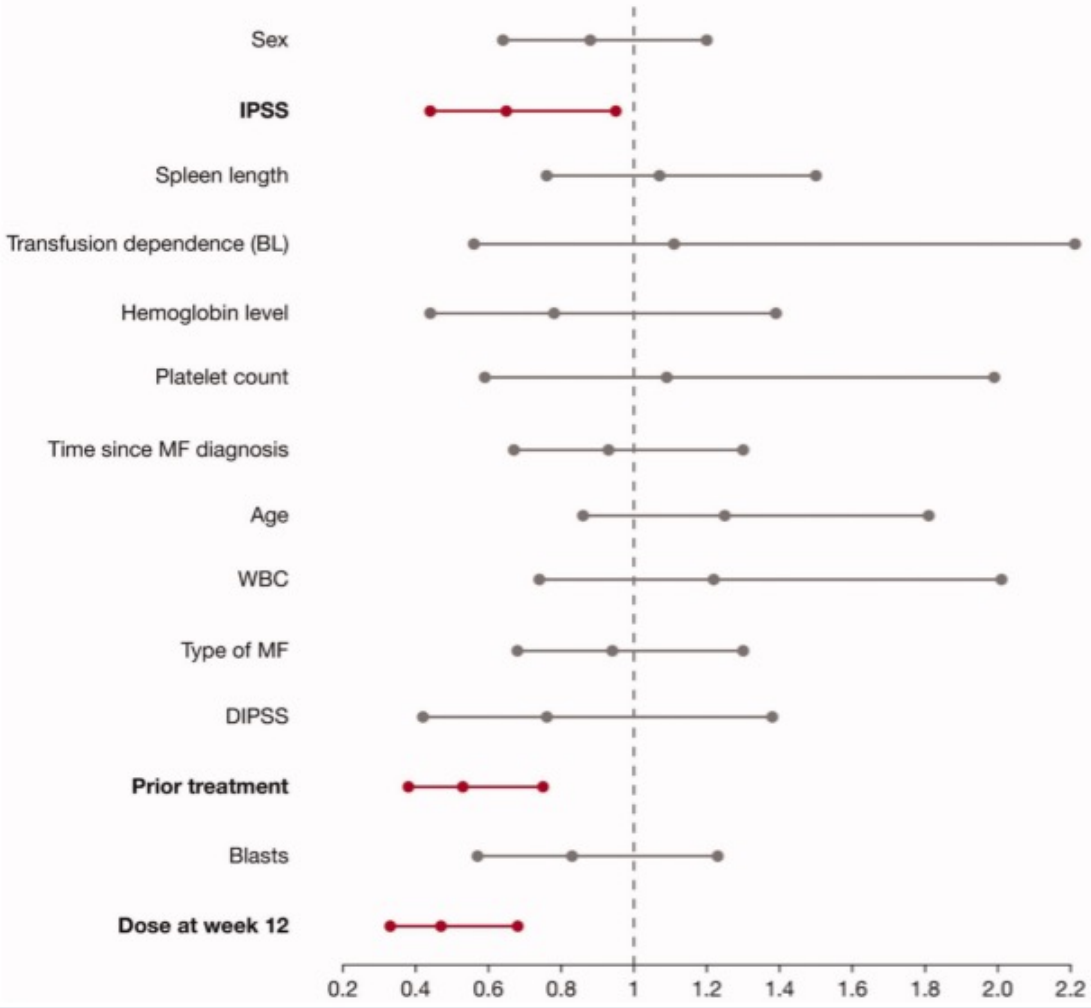
Survival estimate on the basis of RUX-exposure



HR, hazard ratio; MF, myelofibrosis; OS, overall survival; RUX, ruxolitinib.

Verstovsek et al, ASH meeting 2020 abstract 3089

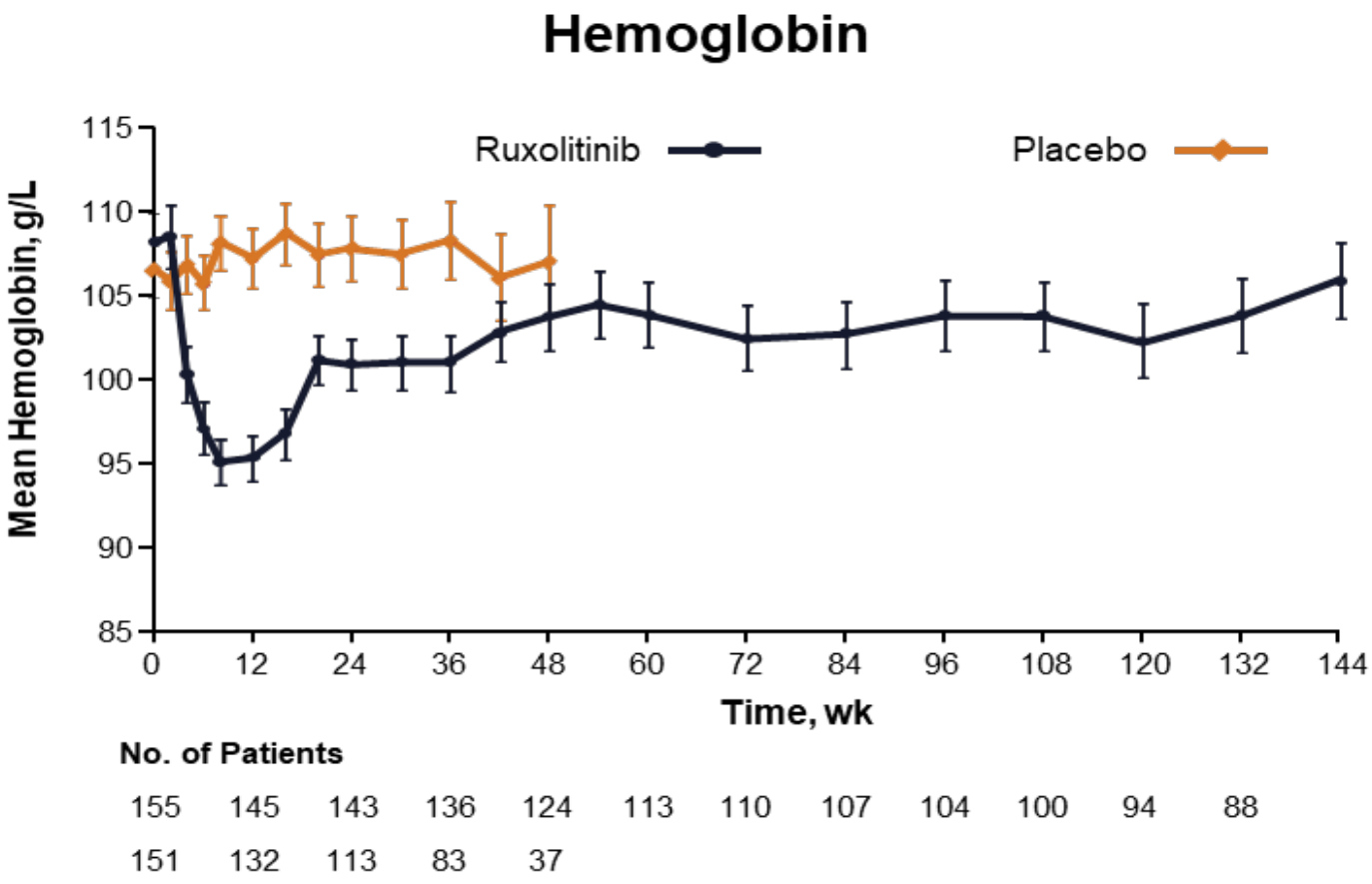
Predictors of response to RUX: JUMP trial



	%	n/N	OR (95% CI)
Male	32.8	354/1079	0.88 (0.64, 1.20)
Female	36.1	318/881	
Intermediate-2/high	30.6	198/647	0.65 (0.44, 0.95)
Intermediate-1/low	43.1	151/350	•
≥ 10 cm below LCM	33.1	462/1394	1.07 (0.76, 1.50)
< 10 cm below LCM	37.1	210/566	
Dependent	29.8	39/131	1.11 (0.56, 2.21)
Not dependent	34.6	633/1829	
< 10 g/dL	28.0	203/725	0.78 (0.44, 1.39)
≥ 10 g/dL	38.0	467/1229	
< 100×10^9/L	23.2	29/125	1.09 (0.59, 1.99)
≥ 100×10^9/L	35.0	641/1829	
> 2 years	30.3	311/1027	0.93 (0.67, 1.30)
≤ 2 years	38.8	360/929	
> 65 years	35.6	377/1060	1.25 (0.86, 1.81)
≤ 65 years	32.8	295/900	
> 25×10^9/L	31.9	111/348	1.22 (0.74, 2.01)
≤ 25×10^9/L	34.8	559/1605	
Primary MF	32.6	379/1162	0.94 (0.68, 1.30)
Secondary MF	36.8	293/797	
Intermediate-2/High	30.0	249/830	0.76 (0.42, 1.38)
Low/Intermediate-1	40.5	324/800	
Second line or beyond	31.5	417/1325	0.53 (0.38, 0.75)
First line	40.2	255/635	•
≥ 1%	30.7	196/638	0.83 (0.57, 1.23)
< 1%	36.9	422/1145	
≤ 20 mg	30.4	206/678	0.47 (0.33, 0.68)
> 20 mg	41.3	466/1127	•

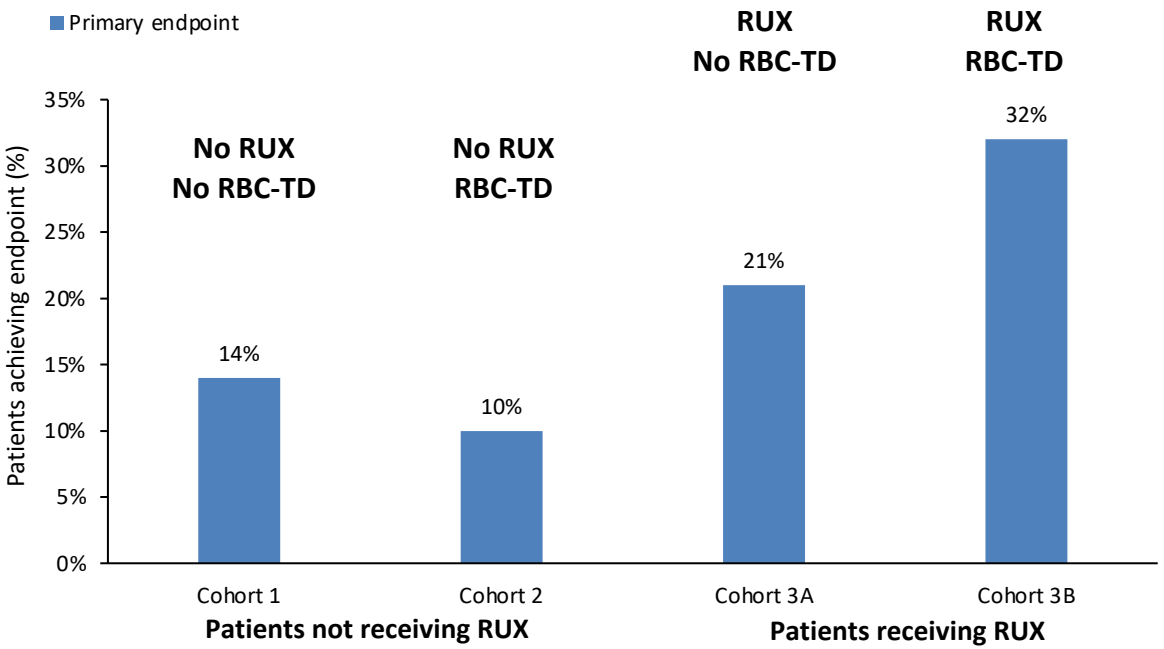
Gupta et al. Leuk Lymphoma . 2020 Nov 19;1-9.

Hemoglobin trend in MF patients receiving RUX



Cervantes et al. Blood 2014.

Luspatercept: primary endpoint achievement in MF patients (ACE-536-MF-001)



For pts not receiving RBC transfusions

- Hb increase ≥ 1.5 g/dL from BL over any consecutive 12-week period without an RBC transfusion

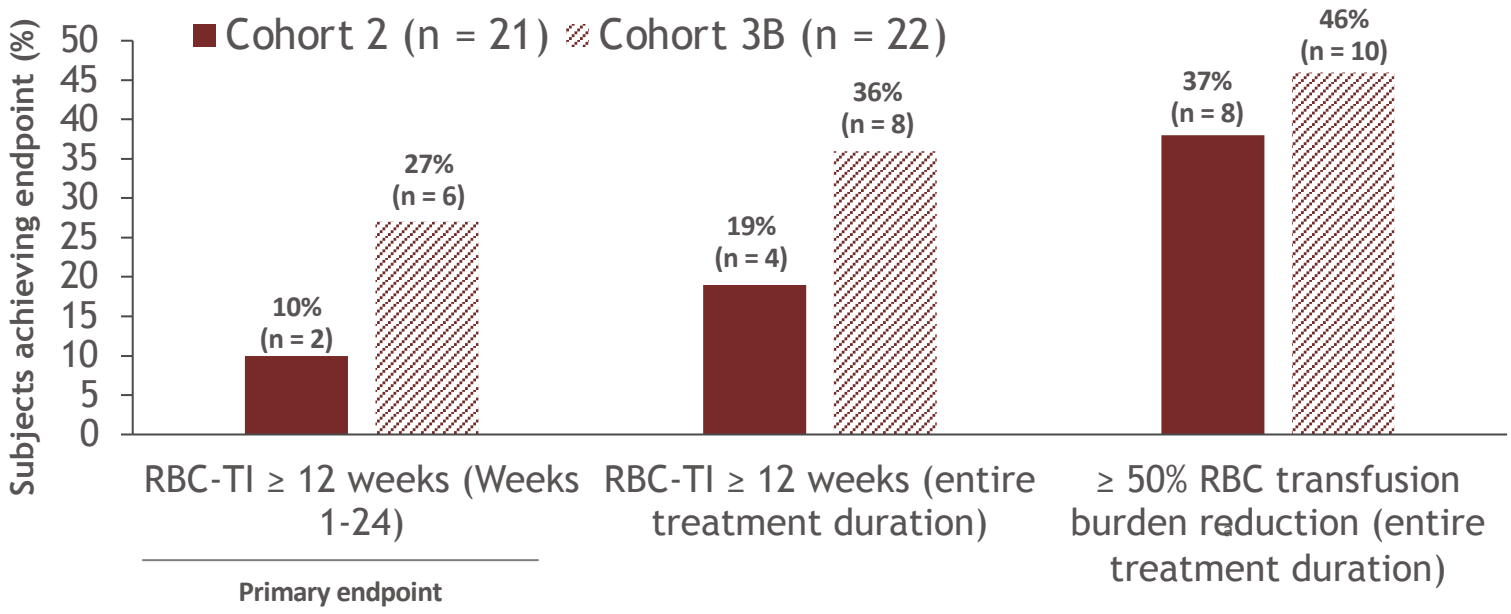
For pts receiving RBC transfusions

- RBC transfusion-free for ≥ 12 consecutive weeks

Gerds et al, ASH 2019, Oral presentation, Abstract n. 557

Luspatercept response in subjects receiving RBC transfusions

- **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

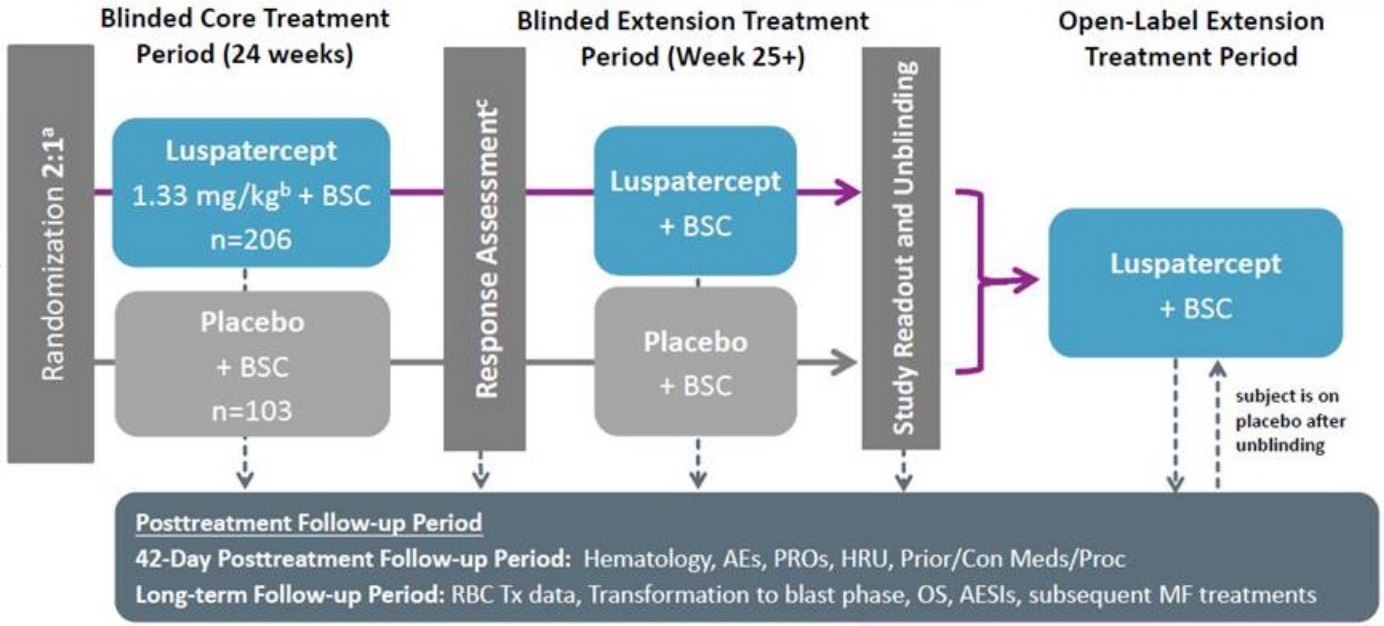
ACE-536-MF-002 - The INDEPENDENCE Trial

A Randomized, Double-blind, Placebo-controlled, Phase 3 Study

Screening (4 weeks)

Key Eligibility Criteria

- MPN-associated MF (PMF, Post-ET MF, Post-PV MF)
- RBC transfusions: 4 – 12 U/12 weeks for:
  - *Symptomatic + Hgb ≤9.5 g/dl*
  - *Asymptomatic + Hgb ≤7 g/dl*
- On JAK2 inhibitor for 32 weeks *(+16-wk stable dose prior to randomization)*
- ECOG: ≤ 2
- Anemia from MPN-associated MF or JAK2 inhibitor therapy
- PB Blast ≤ 5%
- BP < 140/90 mmHg
- Adequate organ functions (cardiac, renal, hepatic)



[a]**Stratification by:**
- Baseline RBC transfusion burden (4 – 5 vs. 6 – 12 RBC U/12 weeks)
- DIPSS (Int-1/Int-2 vs. HR)

[b]**Starting dose** is 1.33 mg/kg every 3 weeks by SC injection, with titration up to 1.75 mg/kg

BSC: includes transfusions, ICT, antibiotic therapies, and nutritional support; excludes ESAs, androgenic steroids and IMiDs

[c]**Response assessment:** continue double-blind treatment if:
- RBC-tx independence ≥ 12 weeks
- Reduced RBC-Tx by ≥ 50% and by ≥ 4 units ≥ 12 weeks up to Response Assessment

Primary Endpt: RBC-Tx free ≥ 12wks starting in 24 wks (RBC-TI 12)
Key Secondary Endpt: RBC-Tx free ≥ 16 wks starting in 24 wks (RBC-TI 16)
Secondary Endpts:
- Duration of RBC-TI 12
- Reduction and duration of reduction in transfusion burden*
- RBC-Tx free ≥ 12/16 wks in Treatment Period
- Change in RBC-transfusion burden
- Cumulative duration of RBC-TI
- RBC-Tx free ≥ 12 wks + mean Hgb increase ≥ 1 g/dL
- Change in serum ferritin from baseline

* Reduced RBC-Tx by ≥ 50% and by ≥ 4 Units ≥ 12 weeks up to day 169

Independence™ In Myelofibrosis Associated Anemia

Fedratinib (FED): a forthcoming option

Clinical trial	Numerosity and trial-specific features	*Fedratinib 400 mg QD*
JAKARTA **FED *vs* Placebo** **(phase 3)**	FED 400 mg QD (n = 96) FED 500 mg QD (n = 97) Placebo (n = 96) JAKi naïve	**SVR35 W24:** 36% **TSS50 W24**: 36% ≥G3 anemia: 43%
JAKARTA-2 **(phase 2)**	FED 400 mg QD (n = 97) RUX resistant/intolerant	**SVR35 W24:** 55% **TSS50 W24:** 26% ≥G3 anemia: 38%

TSS: total symptom score

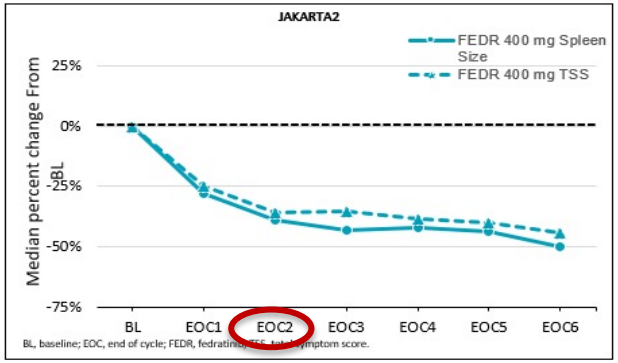
Pardanani et al, JAMA Oncol. 2015;1(5):643-51. Harrison et al, Lancet Haematol. 2017;4(7):e317-24

RUX failure more stringently-defined: a reanalysis of the JAKARTA-2

Ruxolitinib 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

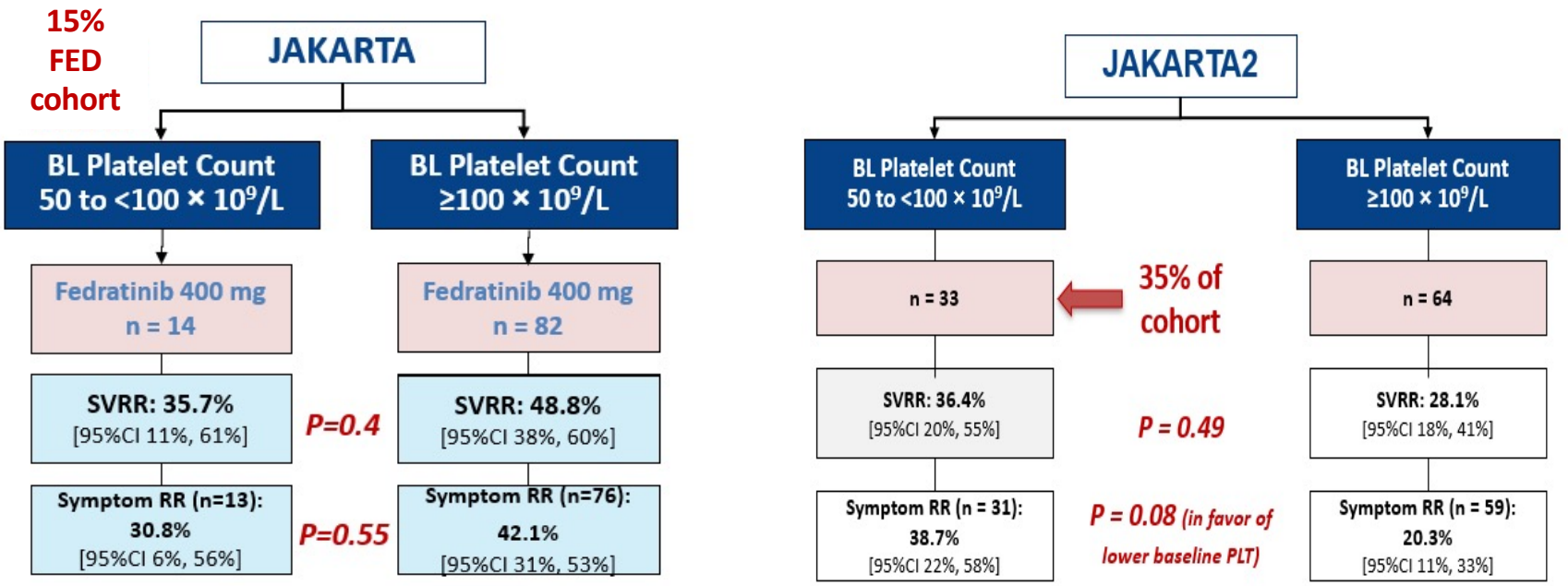
	% of Patients
SVR35 W24	31%
TSS50 W24	27%
G3-4 anemia	38%
G3-4 thrombocytopenia	22%

Rapid responses at end of cycle 2 (EOC2)



Harrison et al, Am J Hematol 2020;95(6):594-603. Passamonti et al, Poster EP1109, EHA 2020

FED is active in case of low baseline PLT count



G3–4 thrombocytopenia: 49% vs 8%

Harrison et al, Oral presentation, Abstract 668, ASH 2019

FED development: ongoing phase 3 studies

- ***Freedom***: A Safety Trial of Fedratinib in Subjects With DIPSS Intermediate or High-Risk PMF, PPV MF and PET MF and Previously Treated With RUX including a Sub-study With Concomitant Luspatercept for Subjects With Anemia

- ***Freedom-2***: An Efficacy and Safety Study of FED Compared to BAT in Subjects With DIPSS-intermediate or High-risk PMF, PPV MF and PET MF and Previously Treated With Ruxolitinib

NCT03755518. NCT03952039

Pacritinib (PAC): outline of the PERSIST trials

Clinical trial	Numerosity and trial-specific features
PERSIST-1 PAC *vs* BAT (excl. JAKi)	PAC 400 mg QD (n = 220) BAT (n = 107) JAKi naïve; any cytopenias
PERSIST-2 PAC *vs* BAT (incl. RUX)	PAC 400 mg QD (n = 104) PAC 200 mg BID (n = 107) BAT (n = 100) JAKi treated or naïve PLT ≤ 100 x 10^9/L BAT included RUX in 45%

Pacritinib

SVR35 in ITT: 19.1%
23% if PLT< 50 x 10^9/L
TSS50 in ITT: 24.5% (PLT ≥ 100 x 10^9/L)
RBC-TI: 25%

AEs: G1-2 gastrointestinal (>90%), G≥3 anemia 17%, G≥3 thrombocytopenia 10%

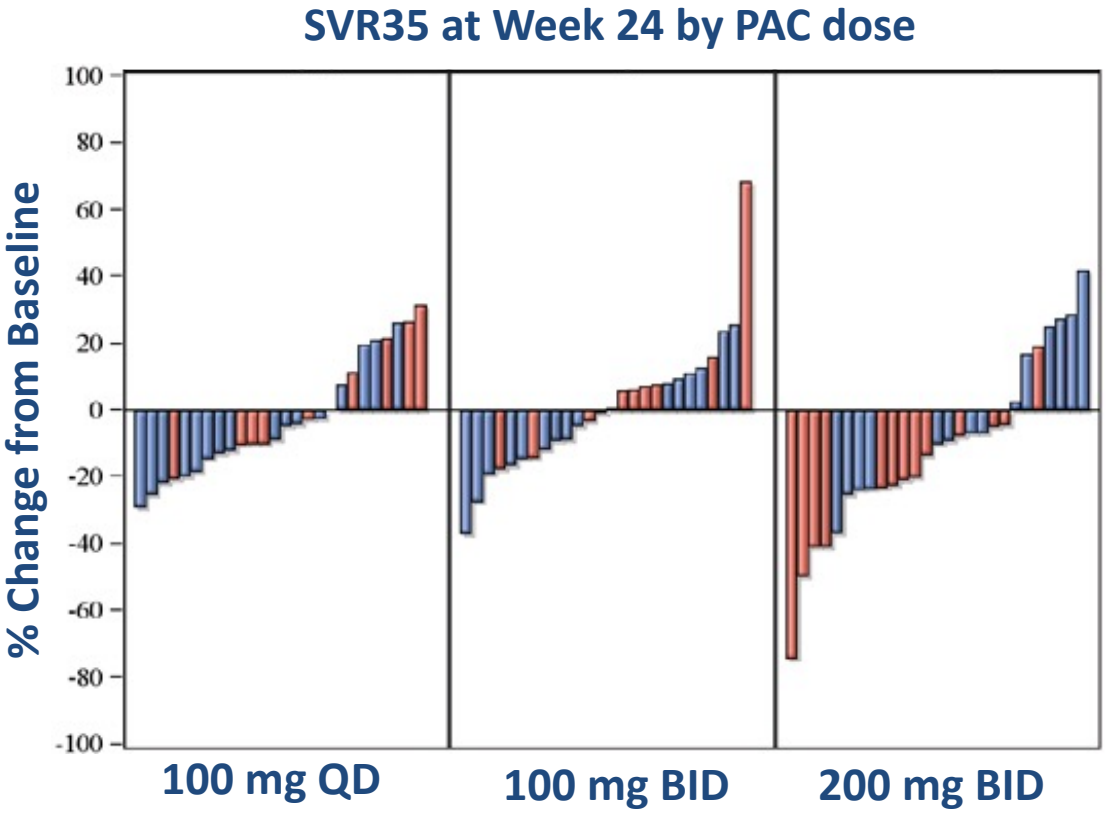
SVR35: 18% (22% PAC 200 mg BID)

TSS50: 25% (32% PAC 200 mg BID)

AEs: diarrhea (48%, G1-2), G≥3 anemia 22%, G≥3 thrombocytopenia 32%

Mesa et al, Lancet Haematol. 2017;4:e225-36. Mascarenhas J, et al. JAMA Oncol. 2018;4(5):652-59

PAC203: a dose finding study in RUX-failure



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%)

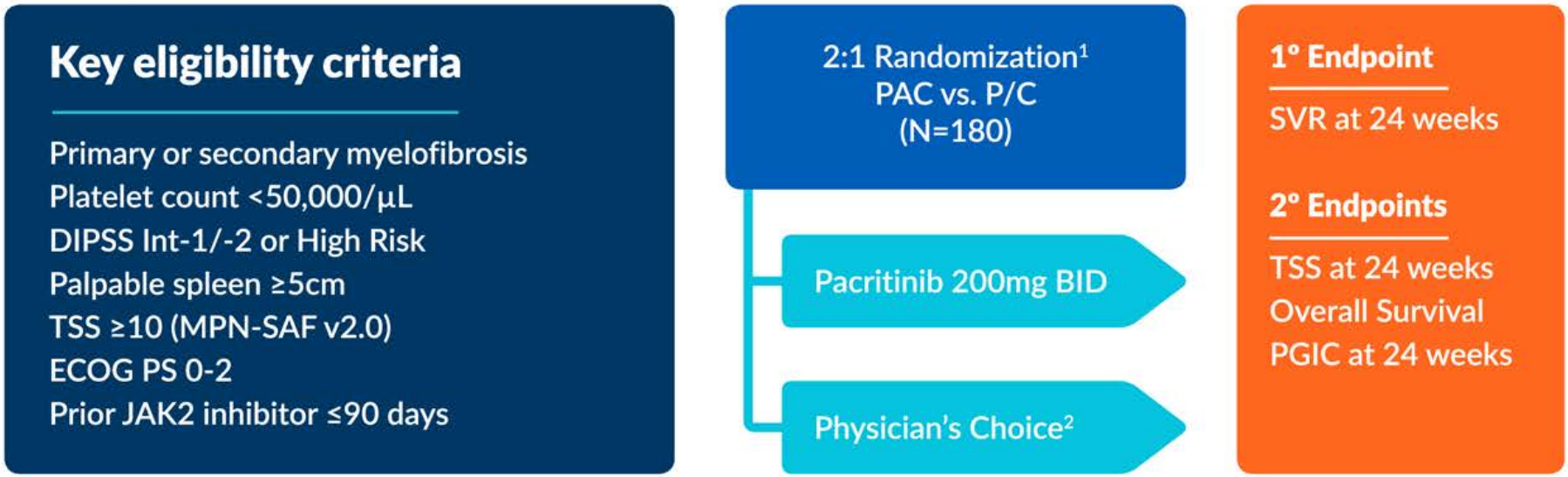
Baseline platelet level

- < 50 x 10^9/L
- ≥ 50 x 10^9/L

PLT count stability over time, independent from baseline values

Gerds et al, Blood Adv.2020;4(22):5825-35.

Pacifica: phase 3 trial for MF patients with PLT <50 x10^9/L and JAKi naive or intolerant



[1]*Cross-over not permitted*

[2]*Physician's Choice (P/C) includes any one of: low-dose ruxolitinib, corticosteroids, hydroxyurea, thalidomide, or lenalidomide*

NCT03165734

Momelotinib (MMB): outline of the studies

- MMB improves inflammatory-mediated anemia by inhibition of Activin A receptor, type 1 (ACVR1)-mediated hepcidin expression in the liver, leading to increased mobilization of sequestered iron from cellular stores and subsequent stimulation of erythropoiesis

Agent	Clinical trial	Numerosity and study-specific features
Momelotinib (MMB)	SIMPLIFY-1 MMB vs. RUX	MMB (n = 215) RUX (n = 217) JAKi naïve
	SIMPLIFY-2 MMB vs. BAT (incl. RUX)	MMB (n = 104) BAT (n = 52) Previously treated with RUX BAT included RUX in 88%

Momelotinib

- SVR: 26.5% (= RUX) – TSS: 28% (<RUX)
- Improvement of transfusion rate and independence

Momelotinib (also in RUX-pre-treated)

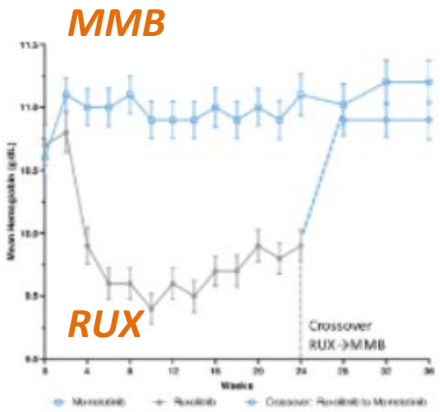
- SVR as BAT

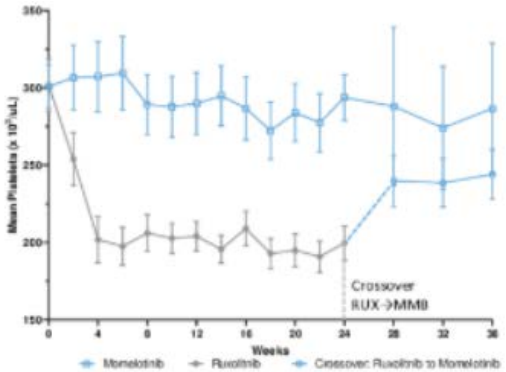
Asshoff M, et al. Blood. 2017 Mar 30;129(13):1823-1830. Mesa RA, et al. Lancet Haematol. 2017;4:e225-e236; Mascarenhas J, et al. JAMA Oncol. 2018; Mesa et al. JCO 2017; Harrison et al, Lancet Hematology 2017

MMB: long term safety data

Simplify 1

HB values



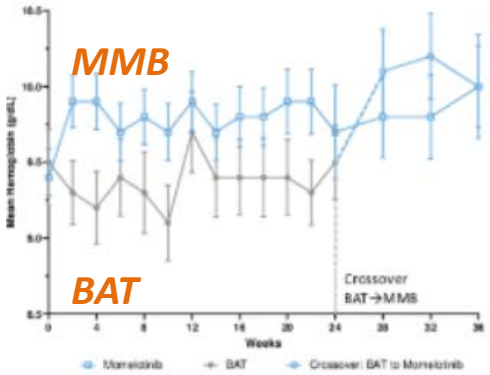


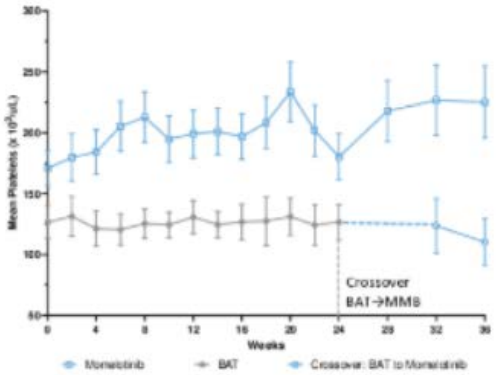
PLT values

Figure 1A and 1B: SIMPLIFY-1 - Mean Hemoglobin and Platelets Over Time

Simplify 2

HB values



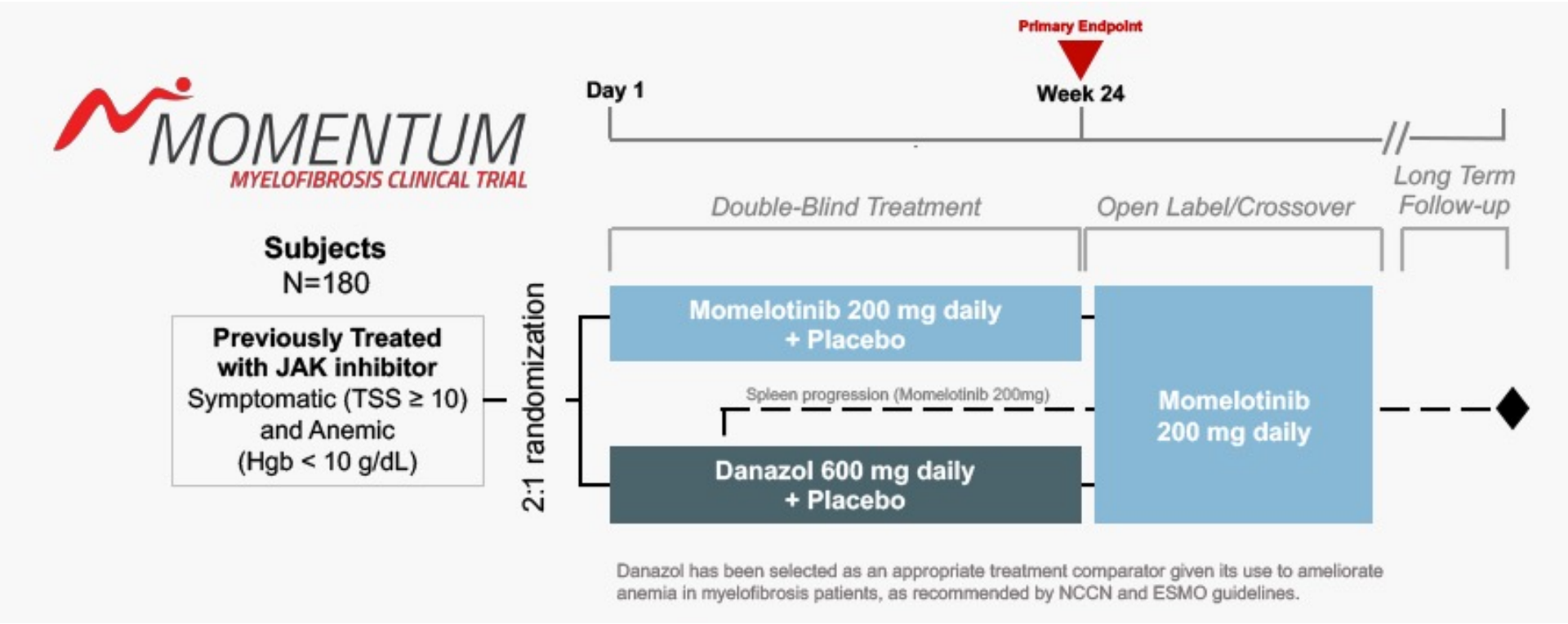


PLT values

Figure 2A and 2B: SIMPLIFY-2 - Mean Hemoglobin and Platelets Over Time

Harrison et al, EHA 2020

MMB: the ongoing phase 3 MOMENTUM trail



- Primary endpoint: TSS reduction at w24
- Secondary endpoints: SVR, anemia response

NCT04173494

Conclusions

- Ruxolitinib is the standard treatment for MF patients
- RUX failure and cytopenias are unmet clinical needs
- FED will be soon available for splenomegaly and symptoms in ruxo-naïve or pre-treated patients
- Pacritinib and momelotinib are under investigation and seem promising for treating cytopenias in MF.
- Many clinical trials active at this time.