Ruxolitinib nella mielofibrosi

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Ruxolitinib: long term clinical data

- 53% of RUX achieves spleen response at any time
- The probability of maintaining a spleen response is 0.51 at 3 years and 0.48 at 5.0 years
- Anemia, thrombocytopenia and infections are the key AEs

JUMP (Int-1R)	163	All grades	**54%**
		Grade 3-4	**24.5%**
COMFORT I (Int-2&HR)	155	All grades	**96%**
		Grade 3-4	**45%**
COMFORT II (Int-2&HR)	146	All grades	**96%**
		Grade 3-4	**42%**

Int-1R

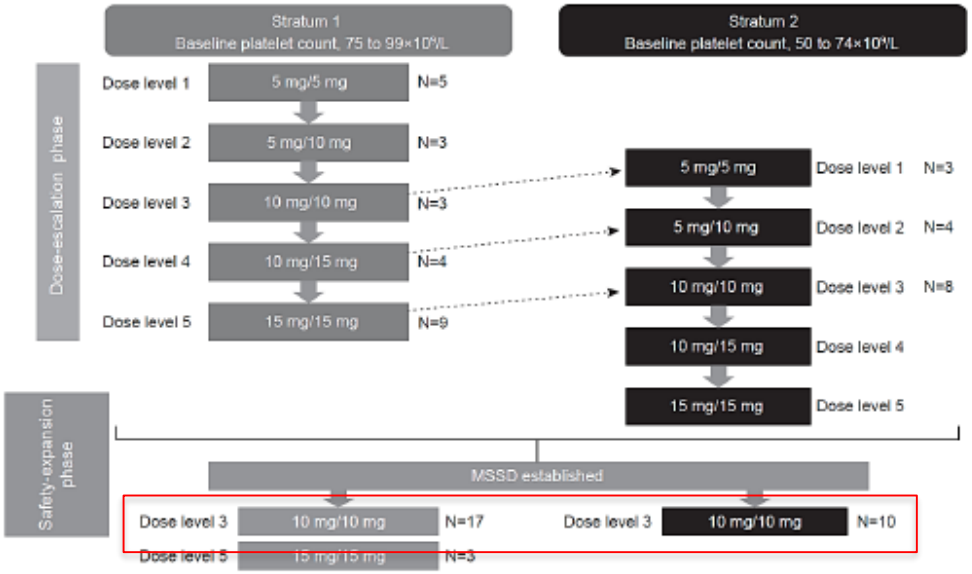
Int-2/HR

Anemia

- 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

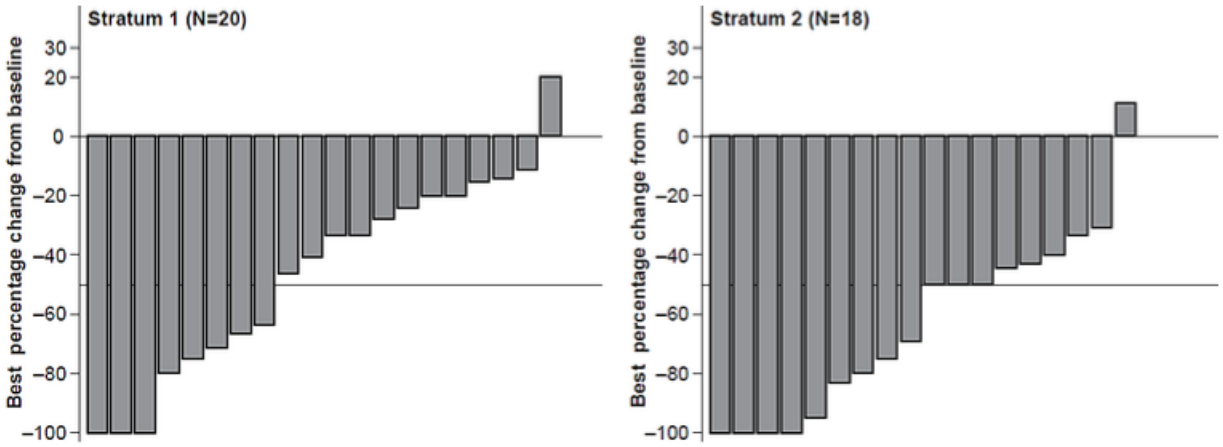
To manage low PLT counts: the EXPAND study



- Stratum 1 (75-99×10^9/L) or stratum 2 (50-74×10^9/L)
- The maximum safe starting dose was 10 mg twice daily in both strata

Spleen response was achieved at w48 in 33.3% and 30.0% of pts in stratum 1 and stratum 2, respectively.

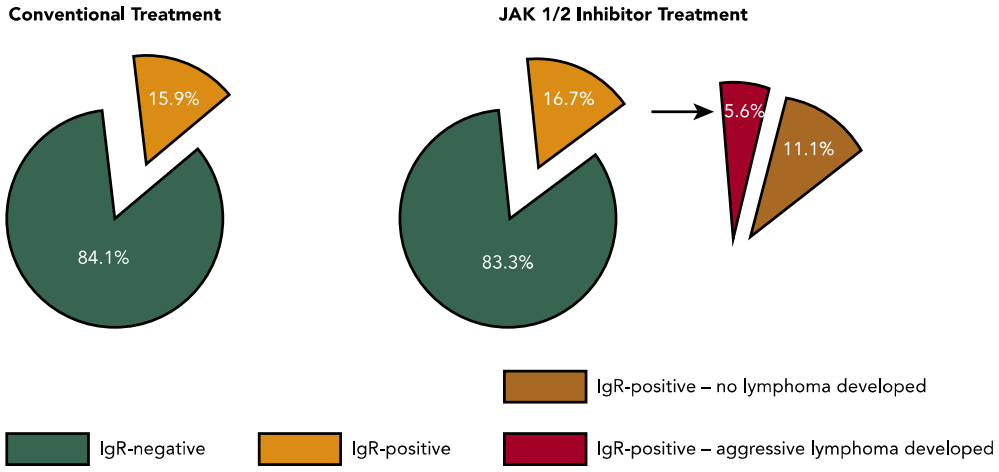
Figure 4. Waterfall plot of best response in spleen length by stratum at MSSD.



Vannucchi AM et al, Haematologica 2018

The case of lymphomas during JAKi

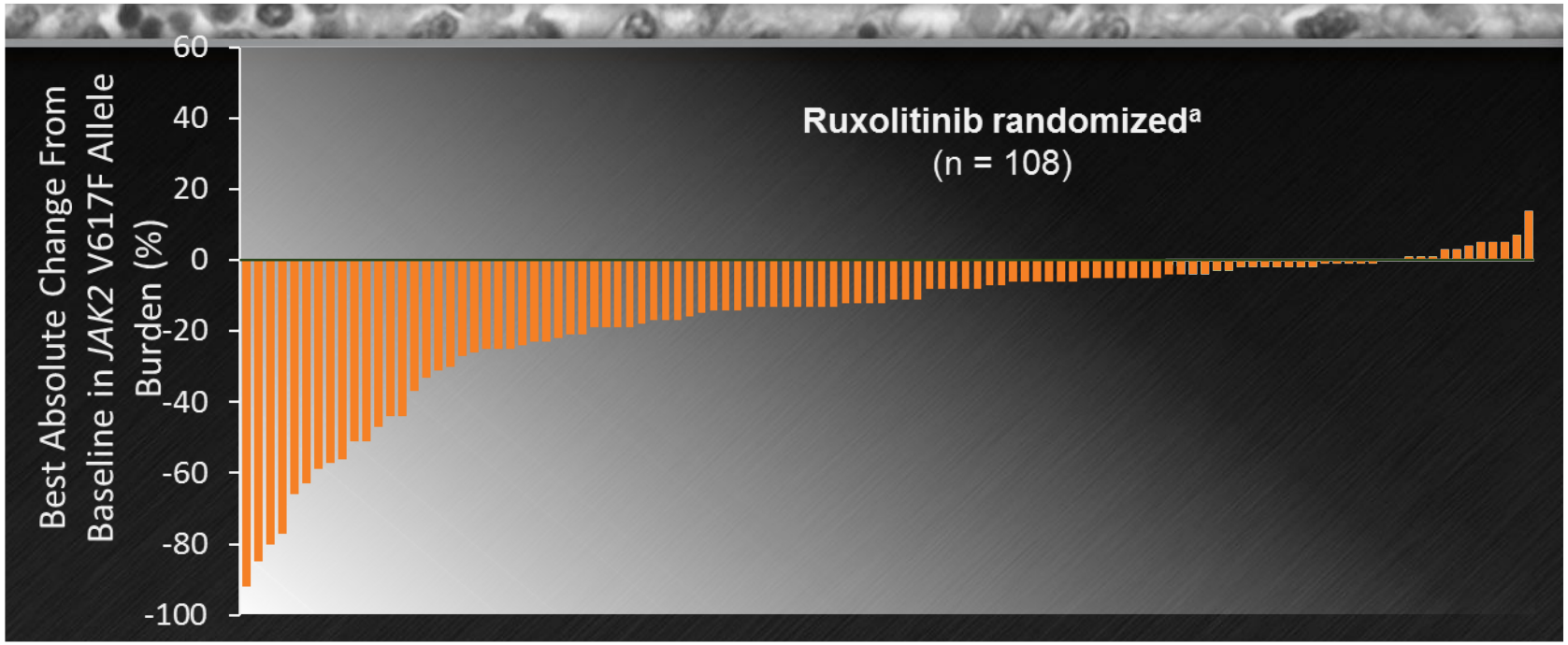
- Among 626 MPNs (69 received RUX), 4 (6%) developed B-cell lymphomas while receiving JAKi and 2 (0.4%) while receiving non JAKi (16-fold higher)
- Lymphomas were of aggressive B-cell type, extranodal, or leukemic with high MYC expression
- Median time from JAKi to NHL was 25 months
- Clonal B cells were present in the BM of 15% of PMF, regardless of treatment



Porpacizy et al. Blood 2018

Ruxolitinib can reduce *JAK2* allele burden in MF

- One-third of evaluable *JAK2* V617F-positive patients had a >20% reduction in allele burden



Harrison et al; Leukemia. 2016 Aug;30(8):1701-7

Long-term effect of ruxolitinib on BM fibrosis

RUX (up to 66 months) effect on BM morphology in 68 patients with advanced MF *vs.* 192 matching patients treated with BAT

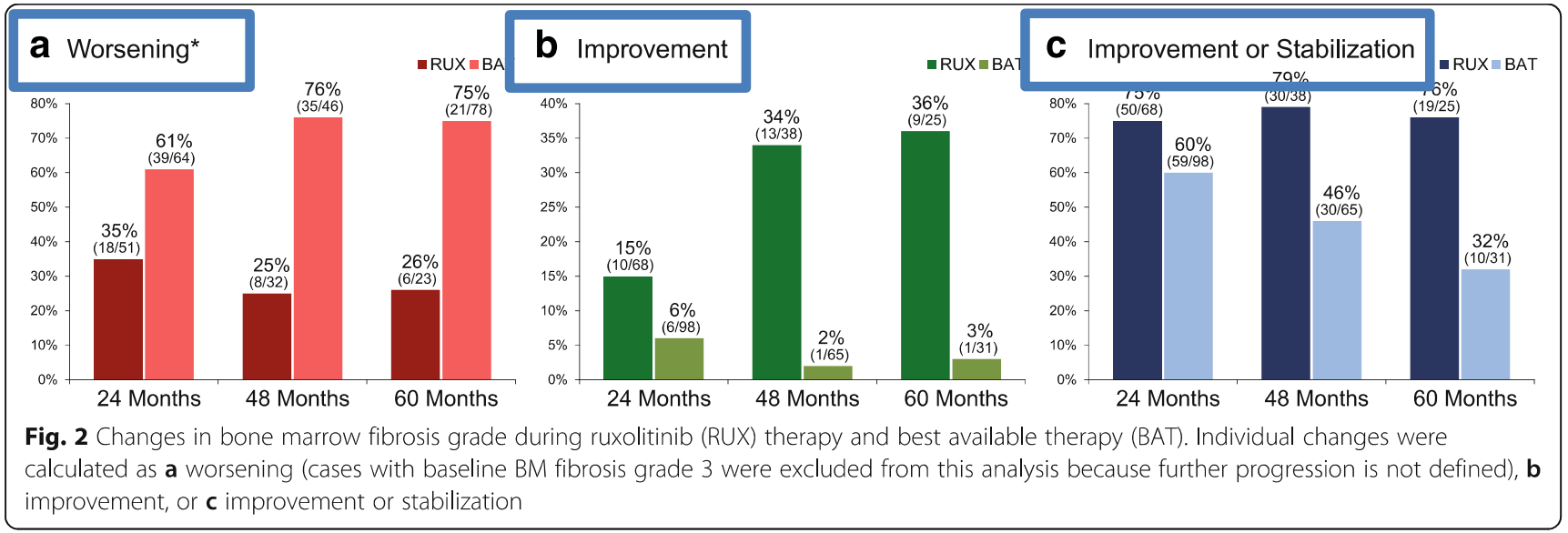


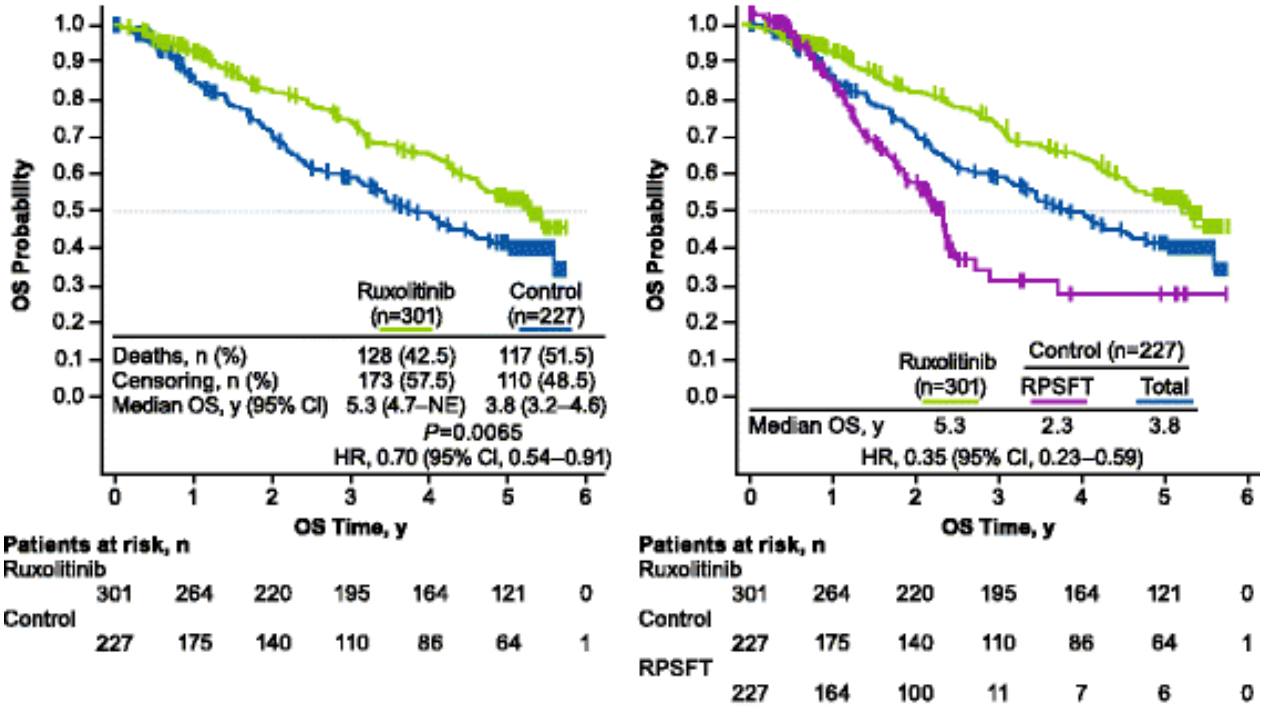
Fig. 2 Changes in bone marrow fibrosis grade during ruxolitinib (RUX) therapy and best available therapy (BAT). Individual changes were calculated as **a** worsening (cases with baseline BM fibrosis grade 3 were excluded from this analysis because further progression is not defined), **b** improvement, or **c** improvement or stabilization

In addition, BM fibrosis reduction was associated with:

- Regression of leukoerythroblastosis
- Durable reduction of circulating blasts

Kvasnicka et al. Journal of Hematology & Oncology (2018) 11:42

Overall survival
analysis of 5-year pooled data from COMFORT-I/II



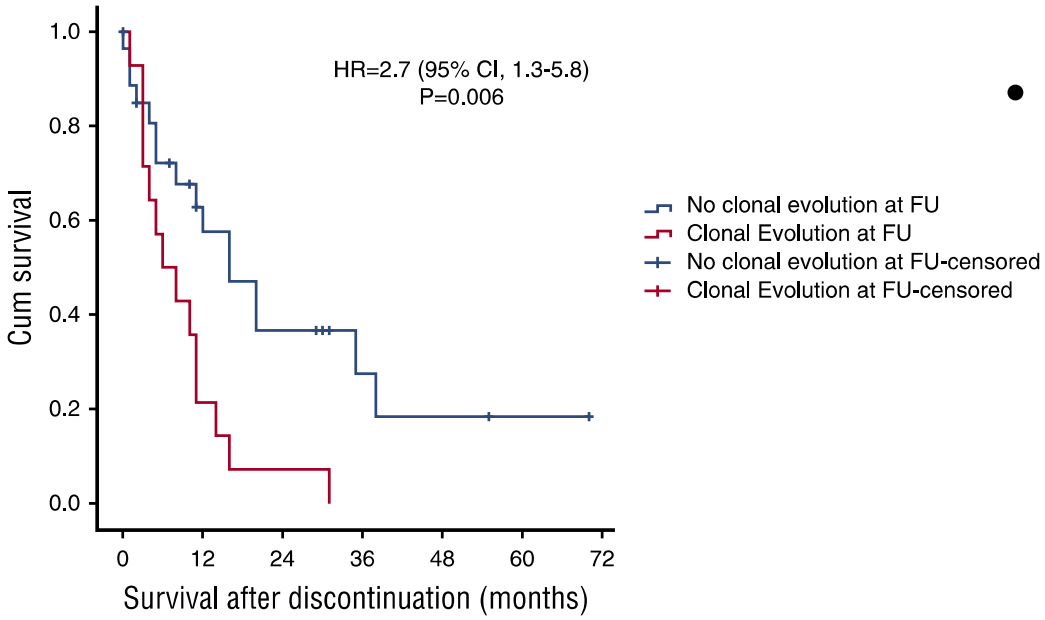
- Ruxolitinib resulted in 30% reduction in risk of death compared to control
- RPSFT (rank-preserving structural failure time, used in oncology to test OS after treatment switching) the OS advantage was more pronounced with ruxolitinib patients compared to control

OS, Overall survival; HR, hazard ratio; CI, confidence interval;
ITT, intention to treat; RPSFT, rank-preserving structural failure time.

Verstovsek et al. J Hematol Oncol. 2016; 127(3):276–8.

RUX discontinuation/failure an unmet clinical need

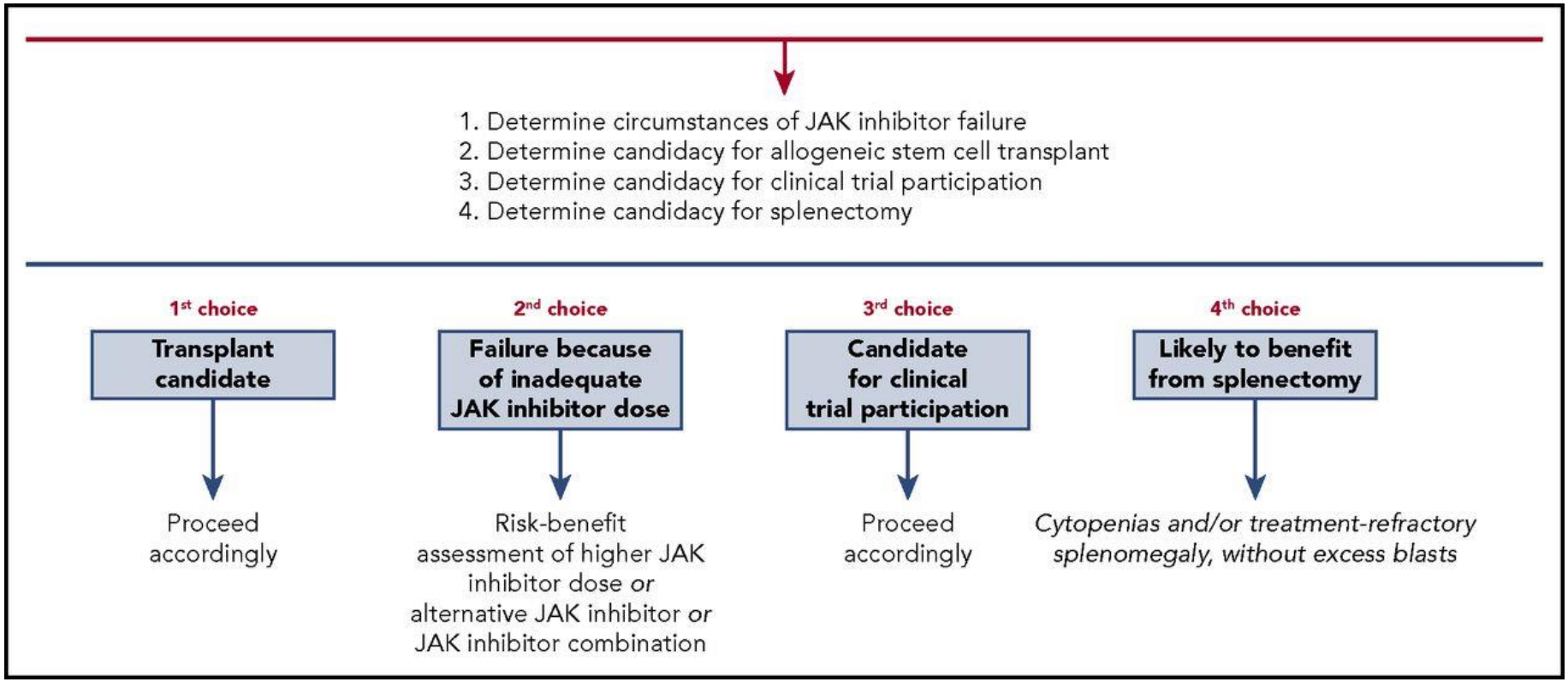
- 86 patients discontinued RUX after a median of 79 months
- Median survival of patients who discontinue RUX is 14 months
- 33% of patients acquired a new mutation at the time of RUX discontinuation (*ASXL1* in 60%)



- Patients with clonal evolution had shorter survival after RUX discontinuation than those without clonal evolution

Newberry et al, Blood 2017

JAKi-failure: a treatment algorithm for MF

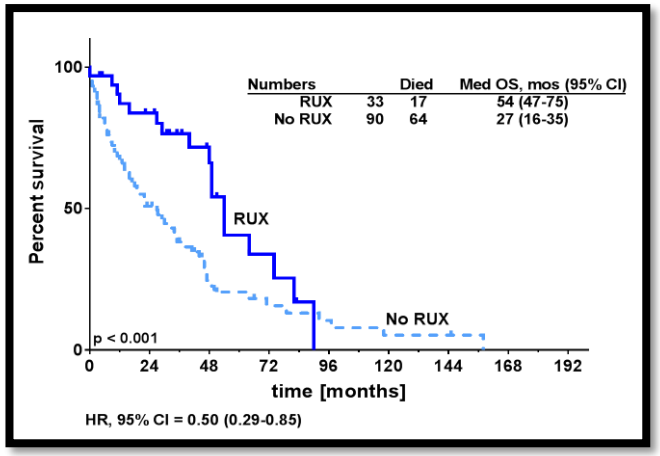


Pardanani and Tefferi Blood 2018;132:492-500

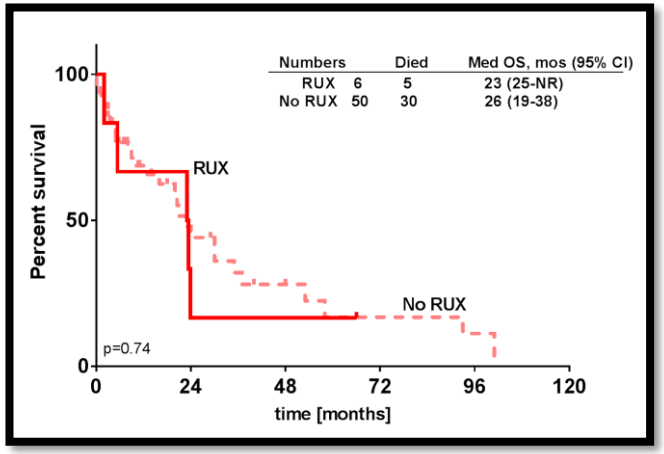
Circulating blasts in MF: an unmet clinical need

- 328 RUX-treated patients: 289 in chronic phase (blasts <5%), 33 in CPe (blasts, 5-9%) and 6 in accelerated phase-AP- (blasts, 10-19%)

MF-CP (BC 5-9%)



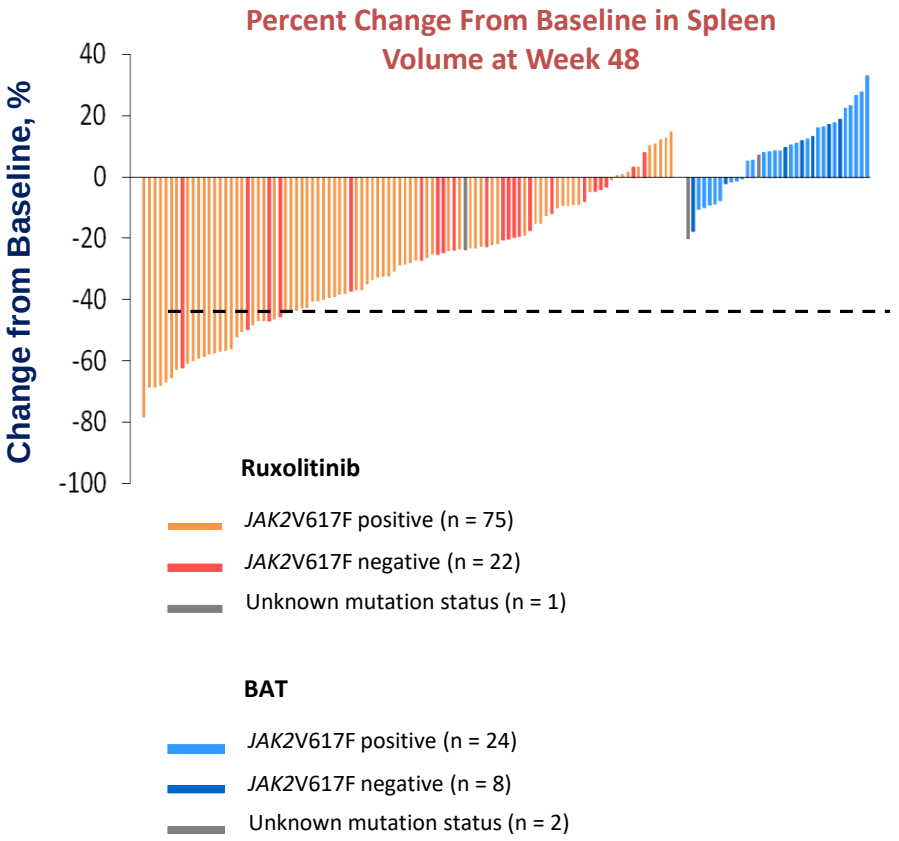
MF-AP (BC 10-19%)

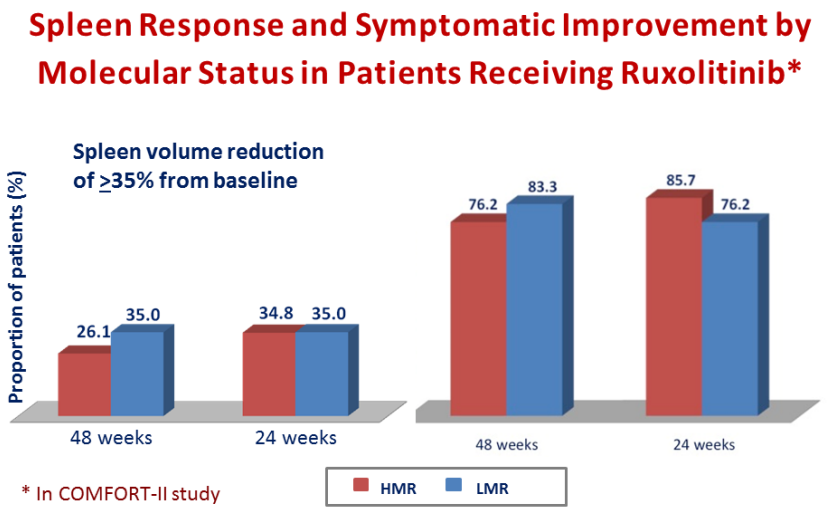


- RUX improves survival in patients with MF and 5-9%-blast cells
- Survival of AP-MF is not increased by RUX

Masarova L et al. Blood 2017 130:201

Ruxolitinib efficacy is genotype-independent





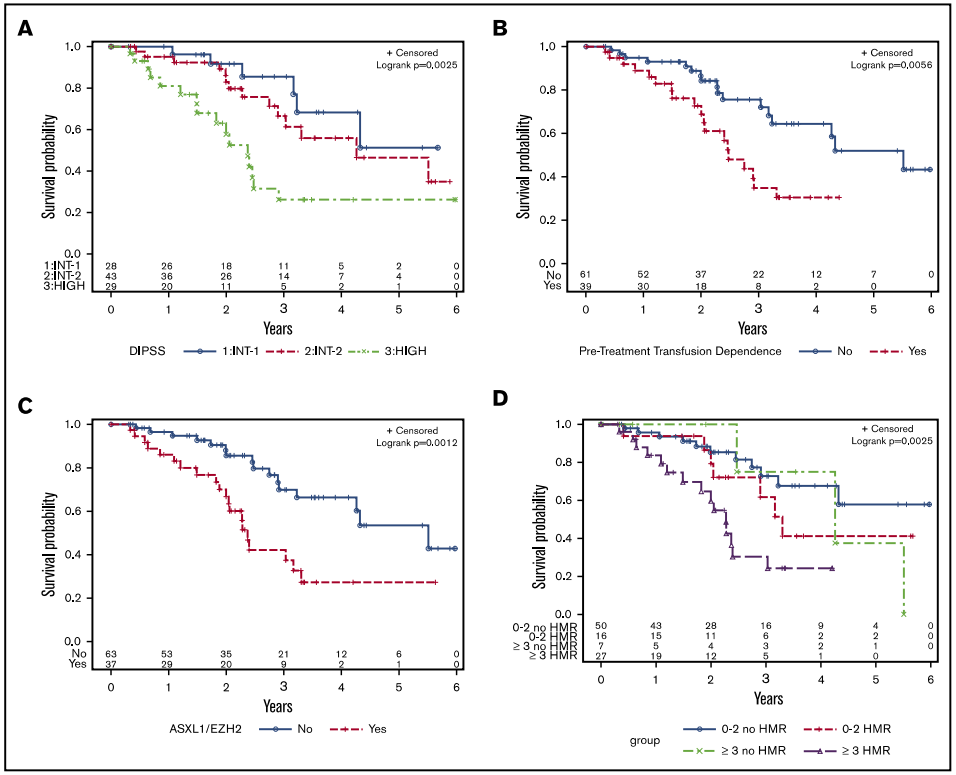
➢ HMR status did not increase the risk of developing anemia or thrombocytopenia under ruxolitinib treatment

Guglielmelli P, et al. *Blood.* 2014; 123:2157-60

Harrison CN, et al. ASH 2011. Abstract 279. Guglielmelli et al, Blood 2014

Single genomic alteration can predict outcomes in MF receiving JAK-inhibitors

- 100 patients: RUX=77; MOME=23
- No mutation was associated with response
- *ASXL1 or EZH2* mutations were independently associated with shorter time to treatment failure
- Impact on survival:



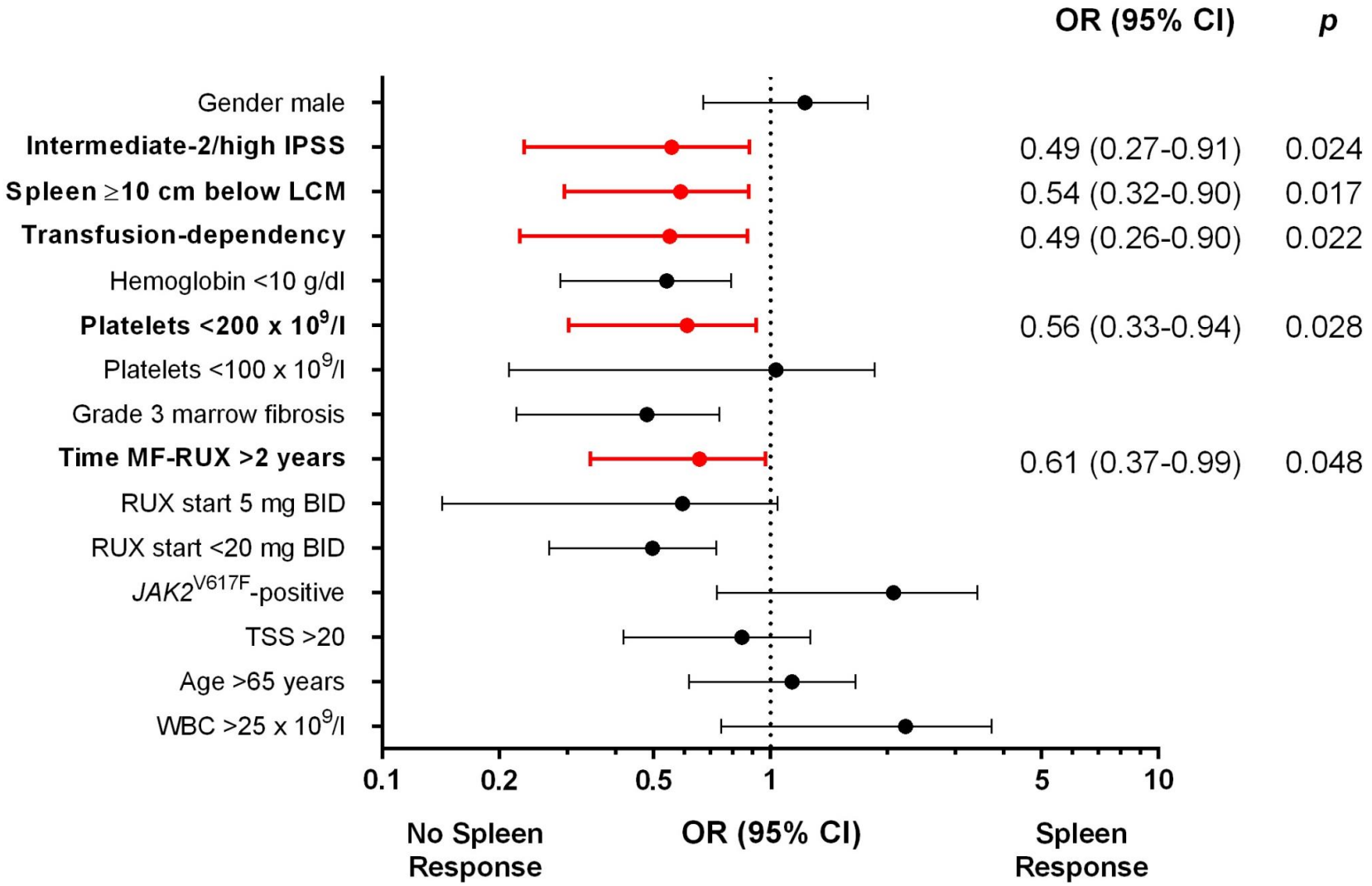
Spiegel et al. Blood Adv. 2017 Sep 8;1(20):1729-1738

JAKi predictors of response (I)

- 548 MF patients treated with JAKi
- Response: 50% decrease in spleen size at early (3–4 months on therapy) and late (5–12 months) timepoints after therapy initiation
- Predictors of early response:
  - Higher doses of JAKi
  - BL spleen size 5–10 cm
  - Hemoglobin
- Predictors of late response:
  - Obtainment of response at the earlier timepoint

Menghrajani et al, Leuk Lymp 2018

JAKi predictors of response (II)

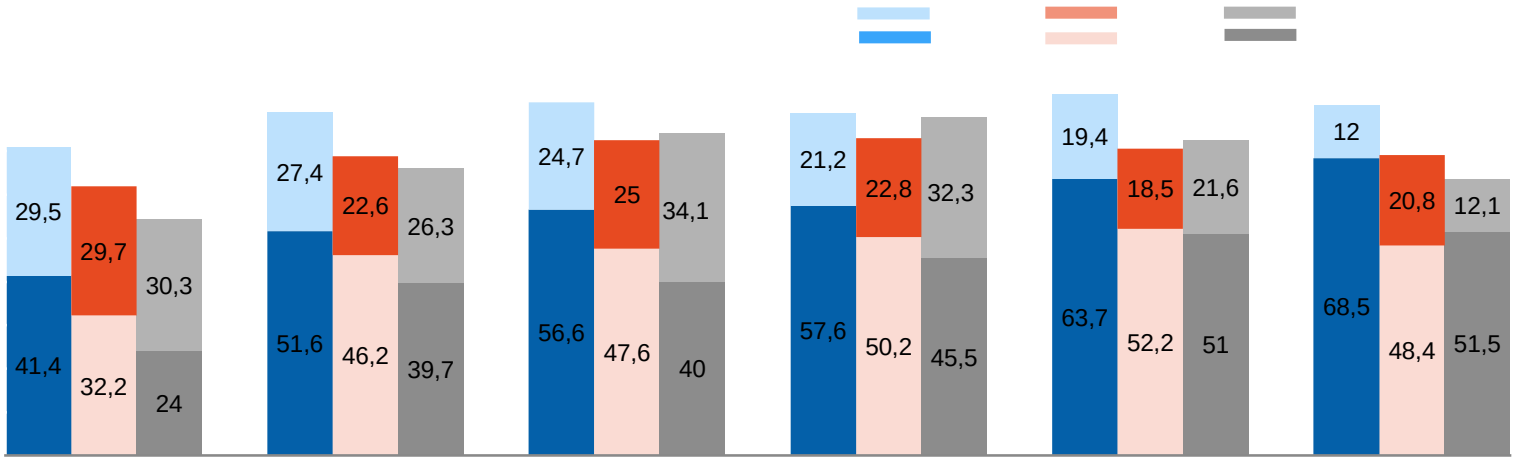


LCM, lower costal margin; OR, overall response; WBC, white blood cell.

Palandri et al. Oncotarget. 2017

JUMP: RUX efficacy per DIPSS stratification

≥ 25% and ≥ 50% reductions from baseline in palpable spleen length

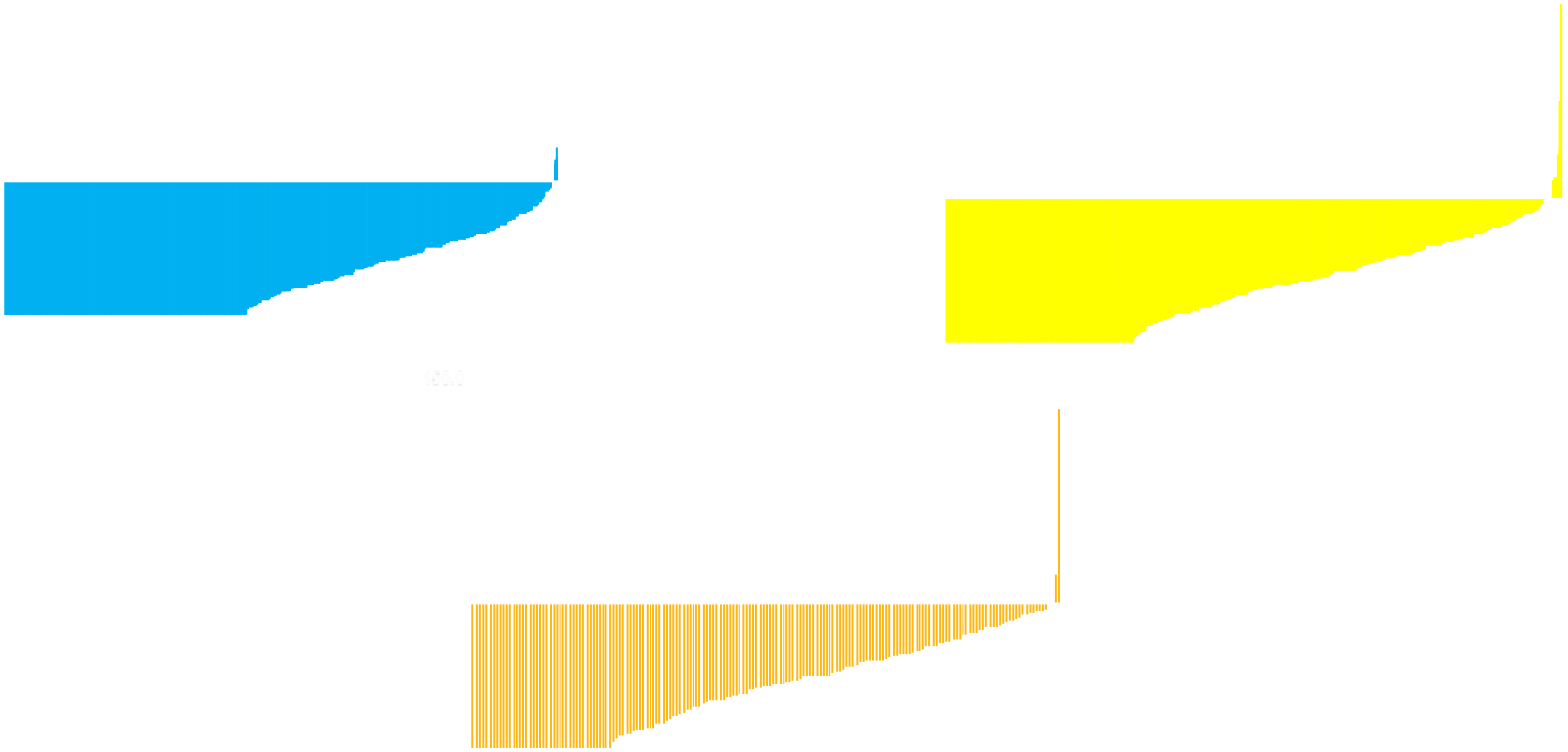


- Number of patients with low-/Int-1–, Int-2– and high-risk MF who achieved ≥ 50% spleen length reduction at any time in the study were 660 (79.5%), 465 (67.1%) and 109 (61.6%), respectively
  - The median time to achieve ≥ 50% reduction in spleen length from BL was 4.7, 7.1 and 8.1 weeks, respectively

BL, baseline; Int-, intermediate; MF,myelofibrosis.

Passamonti et al, EHA 2017

Best spleen response from baseline for each patient at any time during the study



Passamonti et al, EHA 2017

Old and new issues deserving considerations

- ***Anemia and RBC transfusions***
  - Almost all patients develop anemia
  - Manageable, potentially starting at lower doses
  - Occurrence of anemia on RUX does not reduce efficacy on spleen
  - Occurrence of anemia on RUX is not predictive of shortened survival
  - New investigative trials: luspatercept
- ***Limits of platelet count value at baseline > 50 x10^9/L***
- ***Infections***
  - SIE and ELN guidelines* did not suggest any restriction on RUX use

Passamonti & Maffioli Blood 2018;
**Marchetti et al. Leukemia. 2017;31(4):882-888*

Conclusions

- Ruxolitinib is the standard new treatment for MF with a 50% SVR representing the new bar of treatment goals in MF
- Early treatment is an option, that is to be taken into consideration
- Next therapies/combo should improve anti-clonal efficacy, restore normal hematopoiesis and prevent disease progression