How I treat high risk myeloproliferative neoplasms

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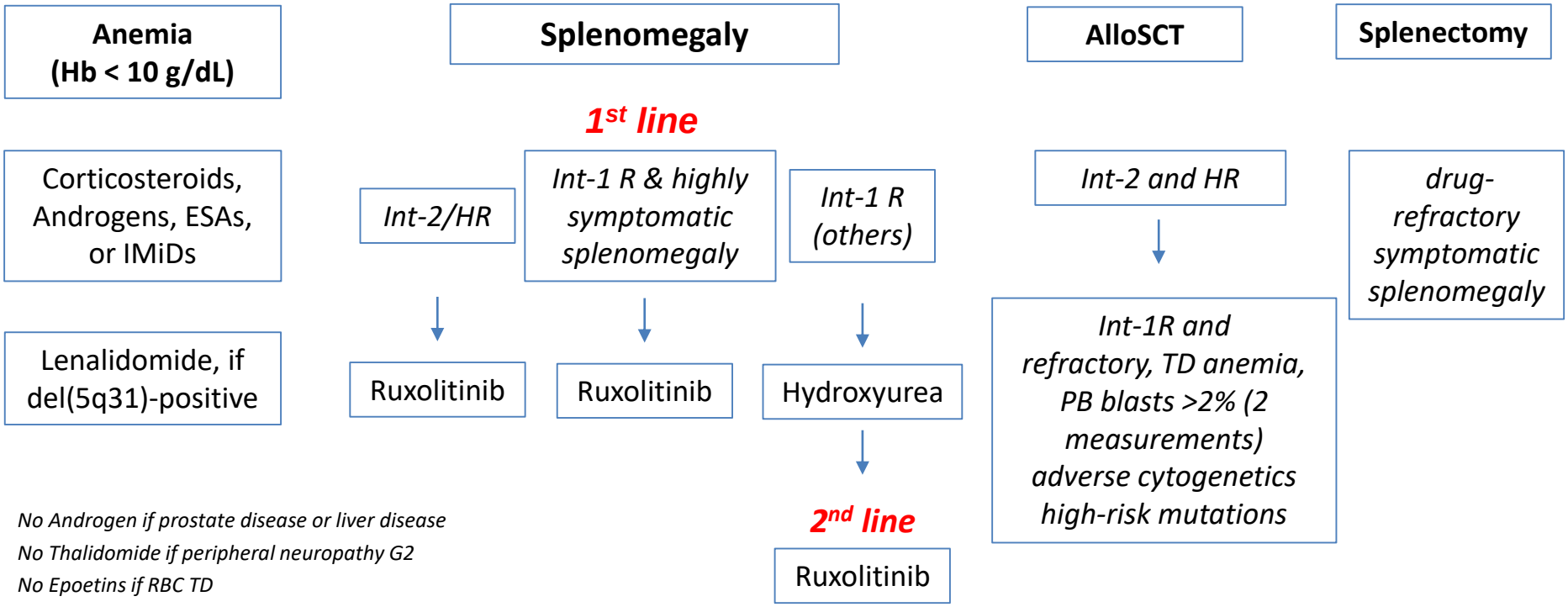
How I treat high risk MF

MF Treatment – ELN 2018 Guidelines

Tiziano Barbui[1] · Ayalew Tefferi[2] · Alessandro M. Vannucchi[3] · Francesco Passamonti[4] · Richard T. Silver[5] · Ronald Hoffman[6] · Srdan Verstovsek[7] · Ruben Mesa[8] · Jean-Jacques Kiladjian[9] · Rüdiger Hehlmann[10] · Andreas Reiter[10] · Francisco Cervantes[11] · Claire Harrison[12] · Mary Frances Mc Mullin[13] · Hans Carl Hasselbalch[14] · Steffen Koschmieder[15] · Monia Marchetti[16] · Andrea Bacigalupo[17] · Guido Finazzi[1] · Nicolaus Kroeger[18] · Martin Griesshammer[19] · Gunnar Birgegard[20] · Giovanni Barosi[21]



No Androgen if prostate disease or liver disease
No Thalidomide if peripheral neuropathy G2
No Epoetins if RBC TD

Hb, hemoglobin; ESAs, Erythropoiesis-stimulating agents; IMiDs, Immunomodulatory agents; Int-1, intermediate-1; PB, peripheral blood; TD, transfusion dependency

Leukemia 2018; 9(8):15–26.

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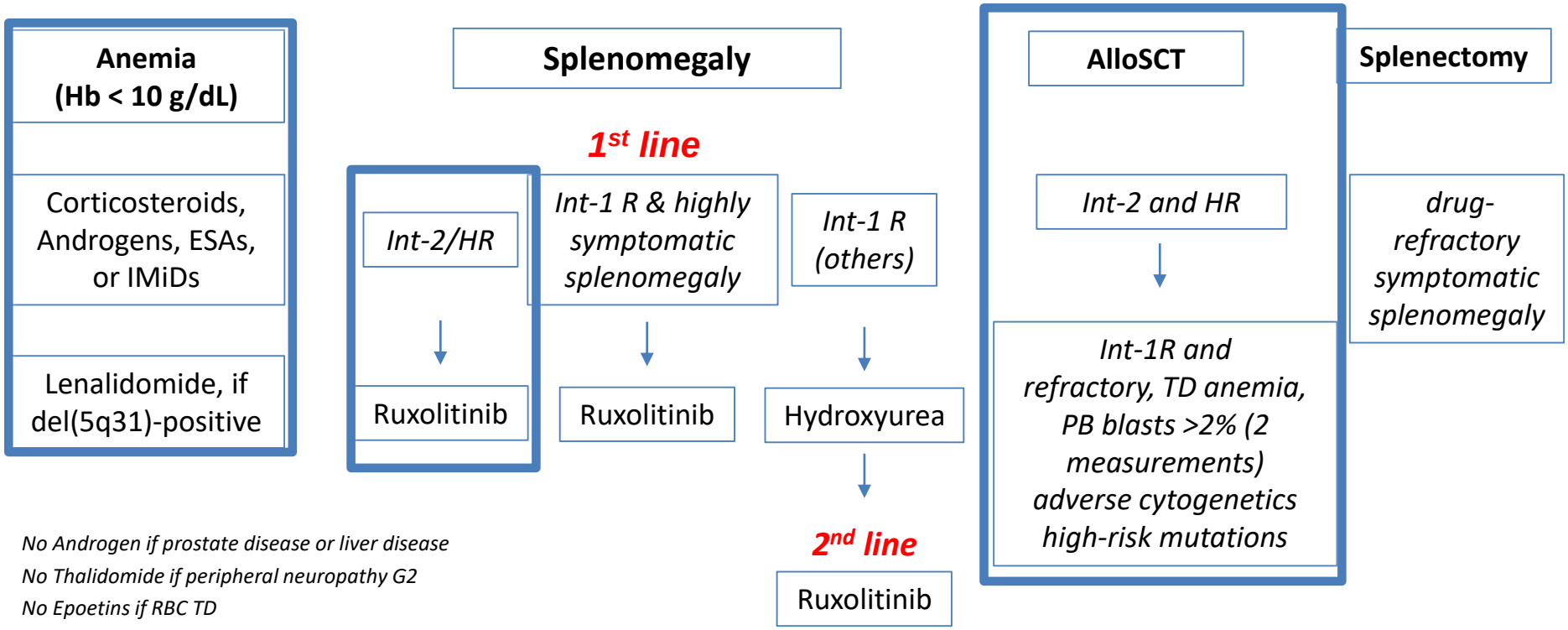

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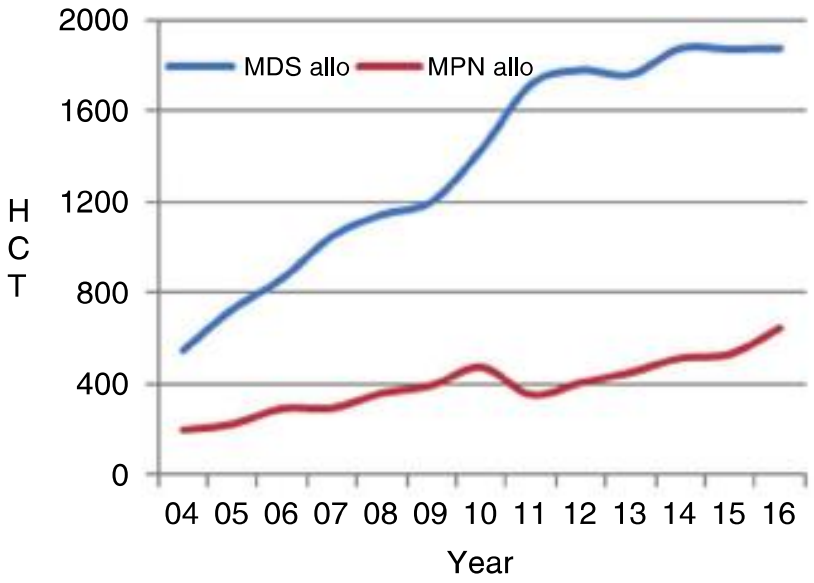
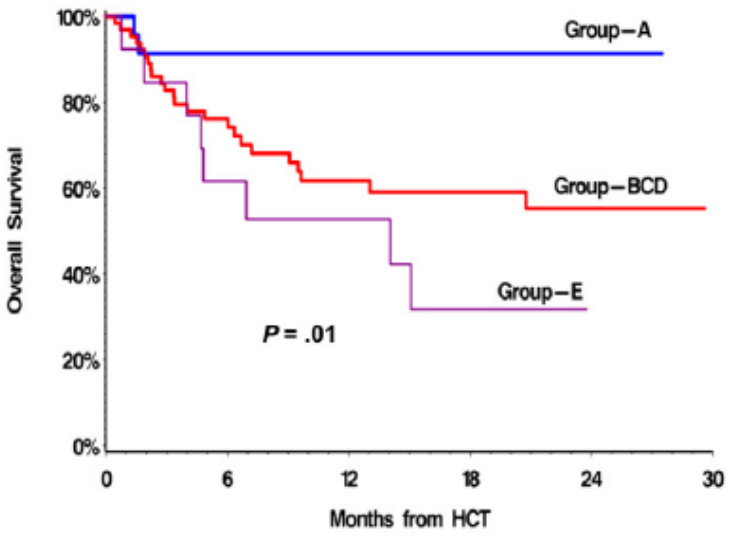
Leukemia 2018; 9(8):15–26.

Stem cell transplant in the JAKi availability

SCT in MPNs (EBMT data)



OS post SCT per JAKi response



- Group A: (23) Clinical improvement
- Group B: (31) Stable disease; Group C: (15) Increase of blast, intolerance for AEs; Group D: (18) progression (new splenomegaly)
- Group E: (13) Blast phase

Passweg et al, BMT 2018; Shanavas et al, BBMT 2016

Ruxolitinib at 5 years follow-up (COMFORT-2)

- 53% of RUX achieved 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

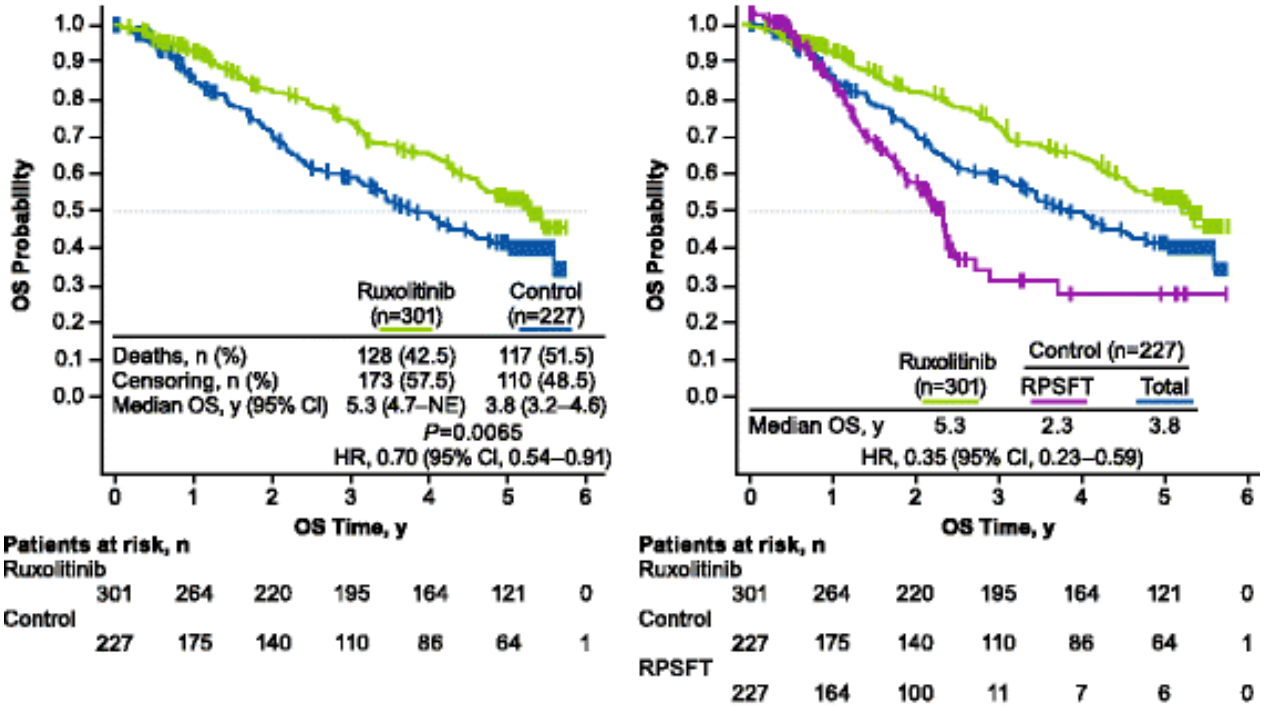
- One-third of evaluable *JAK2* V617F-positive patients had a >20% reduction in allele burden
- 16% improved fibrosis; 32% had stable fibrosis, 18% had a worsening at their last assessment

- AEs grade 3-4: anemia (22%), thrombocytopenia (15%), pneumonia (6%), general physical health deterioration (4%), and dyspnea (4%)

Harrison et al; Leukemia. 2016 May 23

COMFORT-I and -II trials:

Overall survival analysis of 5-year pooled data



- 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.

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
- ***Limits of platelet count value at baseline > 50 x10^9/L***
- ***Infections***
  - SIE and ELN guidelines did not suggest any restriction on RUX use
- ***Resistance***
- ***No prevention of blast phase occurrence***

Passamonti & Maffioli Blood 2018; Verstovsek et al. N Engl J Med. 2012; 366(3):799–807; Gupta et al. Haematologica. 2016; 101(12):e482–e484; Marchetti et al. Leukemia. 2017;31(4):882-888

No clear benefit from RUX-based combinations

	RUXO + panobinostat (HDAC-i) (n = 34)	RUXO + sonidegib (SMO-i) (n = 27)	RUXO + buparlisib (Pi3K-i) (n = 11)	RUXO (mono) (n = 146)
SVR at Wk 24 – ALL	**56.5%**	**44.4%**	**45.5%**	**31.9%**
Thrombocytopenia ≥ Grade 3	29.4%	11%	22.7%	**7.5%**
Discontinuations due to AE	20.6%	18.5%	22.7%	**8.2%**
Additional AE's of concern	Diarrhea, Fatigue	CK increase	Mood disorders	--

Comments on RUX combo vs RUX alone

- Incremental spleen size reduction
- No sign of disease modification
- Safety concerns

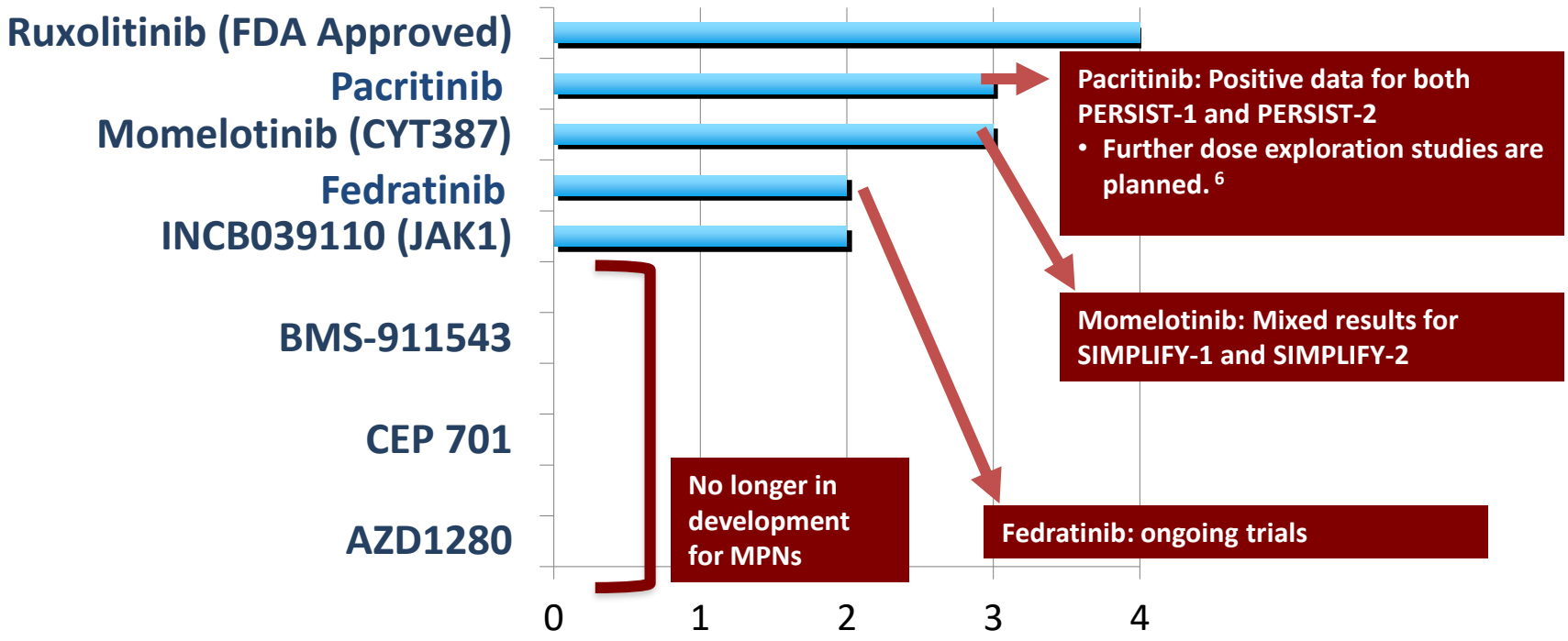
Harrison C et al, ASH 2015, Durrant et al; ASH 2014; Gupta et al, ASH 2015

Other ongoing RUX-based combinations

Class	Agent (combined with RUX)	Target(s)	Phase	Status	NCT.gov identifier
Epigenetic agents	Azacitidine	DNA methylation	2	Recruiting	NCT01787487
	Decitabine	DNA methylation	1/2	Ongoing, not recruiting	NCT02076191
	Pracinostat	HDAC	2	Ongoing, not recruiting	NCT02267278
	Panobinostat	HDAC	1	Ongoing, not recruiting	NCT01433445
	Panobinostat	HDAC	1/2	Ongoing, not recruiting	NCT01693601
Hedgehog pathway inhibitors	Sonidegib	SMO	1/2	Ongoing, not recruiting	NCT01787552
JAKis	Itacitinib	JAK1	2	Recruiting	NCT03144687
Immunomodulators	Thalidomide	Immunomodulation	2	Recruiting	NCT03069326
	Lenalidomide	Immunomodulation	2	Ongoing, not recruiting	NCT01375140
	Pomalidomide	Immunomodulation	1/2	Recruiting	NCT01644110
PI3K/AKT/mTOR pathway inhibitors	INCB050465	PI3K-δ	2	Recruiting	NCT02718300
	TGR-1202	PI3K-δ	1	Recruiting	NCT02493530
Other agents	Ribociclib/PIM447	CDK4/6 inhibitor Pan-PIM kinases	1	Ongoing, not recruiting	NCT02370706
	PU-H71	HSP90	1	Recruiting	NCT03373877
	Pevonedistat	NAE	1	Not yet recruiting	NCT03386214
	Sotatercept	ActRIIA ligands	2	Recruiting	NCT01712308
	Luspatercept	ActRIIB ligands	2	Recruiting	NCT03194542
	Peg-IFN α-2a		1/2	Recruiting	NCT02742324

Passamonti & Maffioli Blood 2018.

Status of development of JAKi in MF



Verstovsek S, et al. *Blood.* 2016;128: Abstract 3110; Mesa RA, et al. *Lancet Haematol*. 2017;4(5):e225-e236; Mascarenhas J, et al. *Blood.* 2016;128(22). Abstract LBA-5; Mesa RA, et al. ASCO Annual Meeting, June 6, 2017; Abstract 7000.; Harrison CN, et al.. ASCO Annual Meeting, June 6, 2017; Abstract 7001; Bose P, Verstovsek S. *Blood.* 2017;130(2):115-125; Mascarenhas JO, et al. *Haematologica* 2017;102:327-35; Verstovsek S, et al. *Leukemia* 2017;31:393-402; Bose P, et al. *Exp Opin Invest Drugs* 2017;26(6):723-734

Pacritinib in RUX-*naïve* (PERSIST-1 vs BAT)

- SVR: 19% *vs.* 5%, irrespective of baseline PLT
- TSS response rates: 25% *vs.* 7%
- 26% of RBC-TD became RBC-TI with PAC
- Adverse events: diarrhea, nausea, and vomiting

Pacritinib also in RUX-pretreated (PERSIST-2 vs BAT)

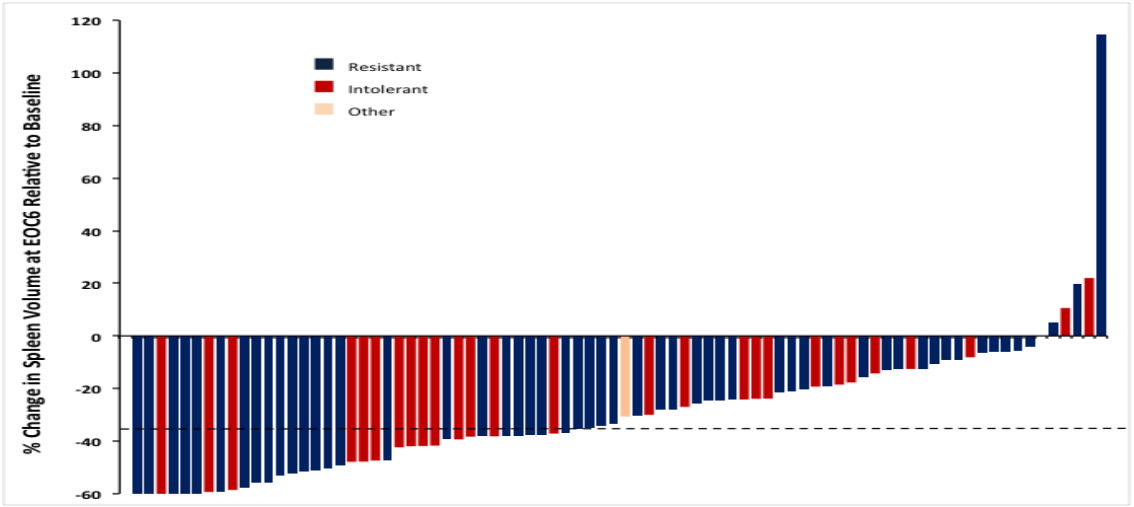
- SVR: 18% (PAC) *vs.* 3% (BAT)
- TSS response rates: 25% (PAC) *vs.* 14% (BAT)
- AEs: gastrointestinal and hematologic; cardiac in 7% (PAC BID), 13% (PAC QD), and 9% (BAT); intracranial hemorrhage 1% (PAC QD)

Mesa RA, et al. Lancet Haematol. 2017;4:e225-e236; Mascarenhas J, et al. JAMA Oncol. 2018

Fedratinib in RUX-*naïve* (JAKARTA *vs.* PBO)

- SVR: 36% (FED 400 mg)
- Reduction in TSS ≥ 50%: 36% (FED 400 mg)
- G3/4 anemia, thrombocytopenia (43%, 17%); GI toxicity (G1/2); Werniche's encephalopathy in 4/97 pts (FED 500 mg)

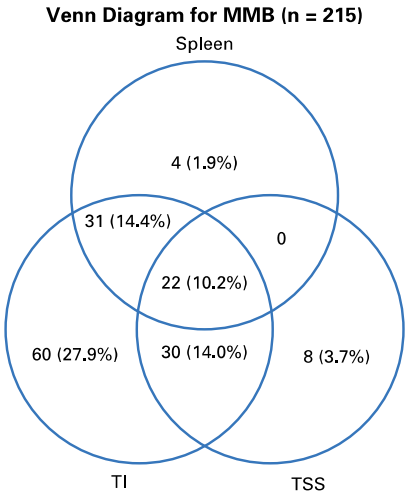
Fedratinib in RUX-failure (JAKARTA-2)

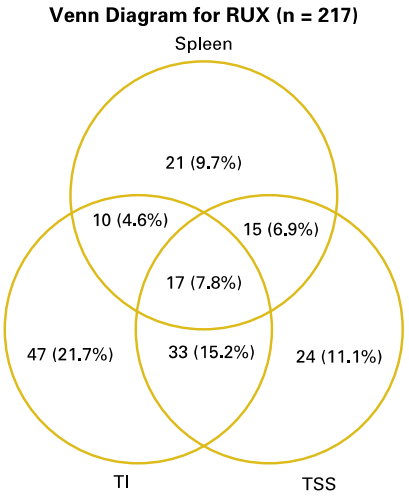


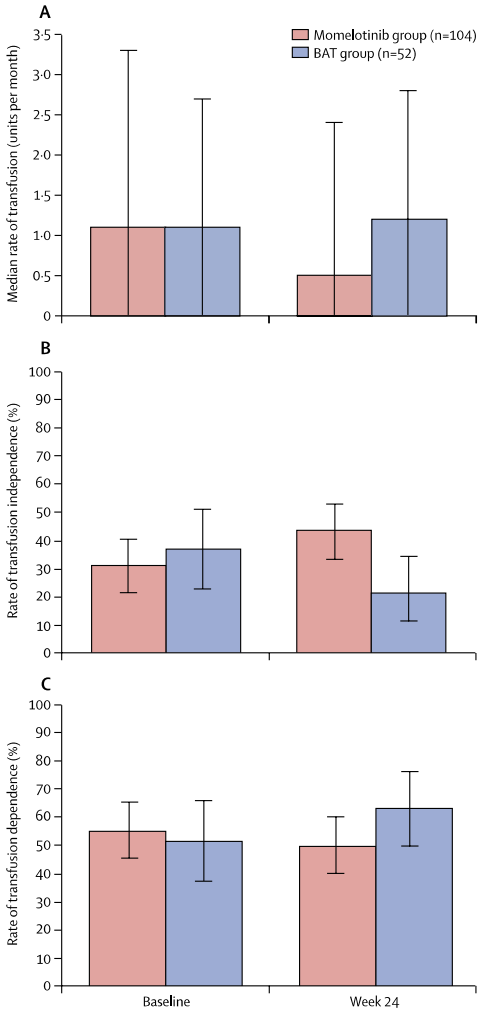
SVR in 55% of RUX-failed patients

*Pardanani et al. JAMA Oncol. 2015; *Harrison et al, ASH 2017; Harrison et al. Lancet Haematol. 2017*

Momelotinib in RUX-*naïve* (SYMPLIFY-1, *vs.* RUX) and in also RUX-pretreated (SYMPLIFY-2, *vs.* BAT)







Rate of transfusion

Rate of RBC transf. Independence

Rate of RBC transf. dependence

Mesa et al. JCO 2017; Harrison et al, Lancet Hematology 2017

Can we personalize the use of JAKis in MF patients?

- No comparison among JAKi is feasible (no head to head comparison, moderate differences in baseline features (rate of SMF, entry platelet count, spleen size)
- All patients entering these trials were in advanced phases of MF and most received HU before enrollment

- RUX, FED seem very active on splenomegaly
- All JAKis tackle symptomatology (RUX most effective)
- PAC and MOME seem attractive for cytopenic patients
- FED is extremely active after RUX-failure

Passamonti & Maffioli Blood 2018.

How I treat high risk PV

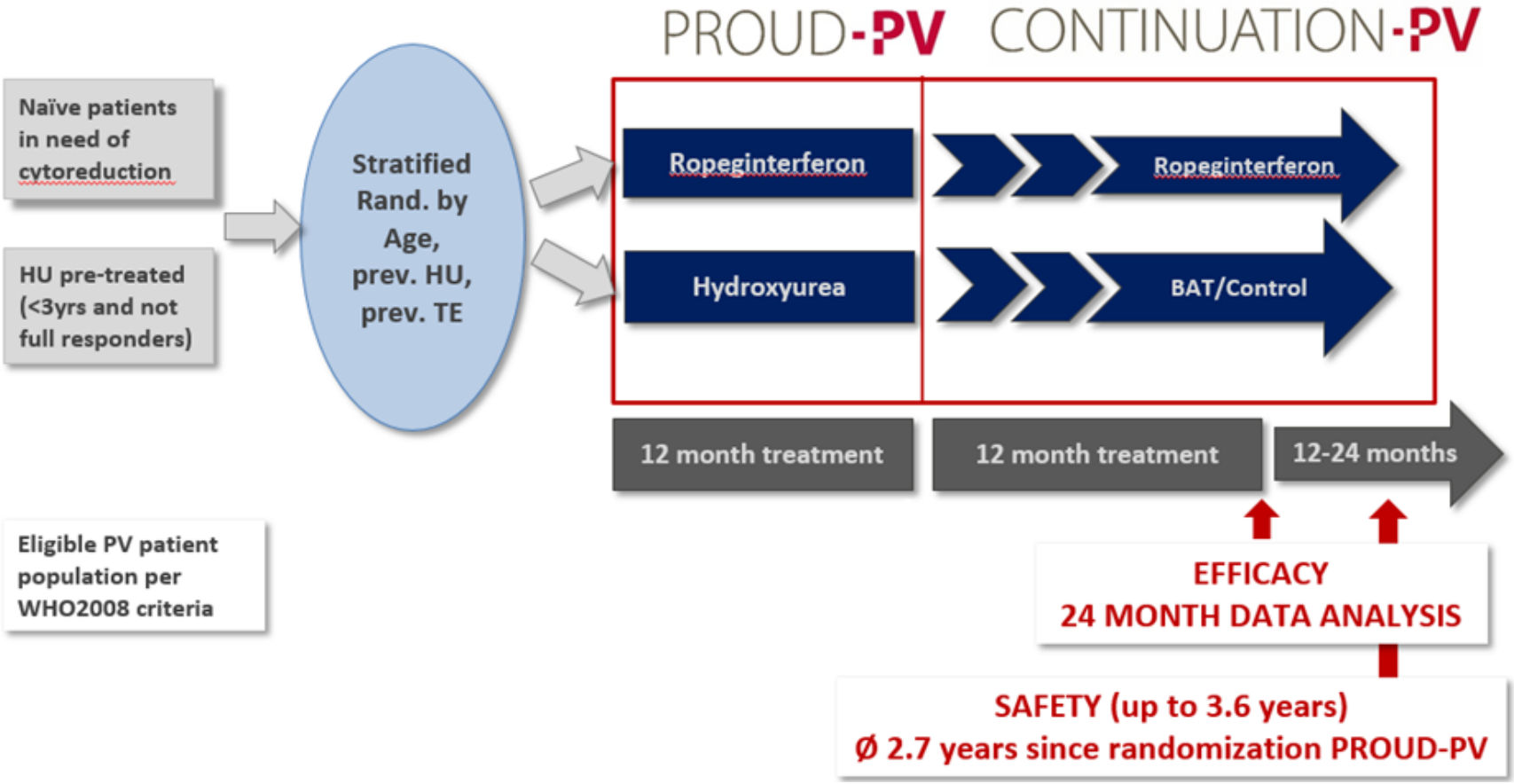
PV: the 2018 ELN recommendations

Polycythemia vera

- Phlebotomy to maintain the HCT <45% & daily LD aspirin
- Cytoreduction in high-risk, or hyper-myeloproliferative, or phlebotomy poorly-tolerant patients
  - Either hydroxyurea or rIFNα is the first-line
  - Both rINFα and ruxolitinib are appropriate second-line therapies for intolerant or inadequately HU responding PV

Barbui et al, Leukemia 2018

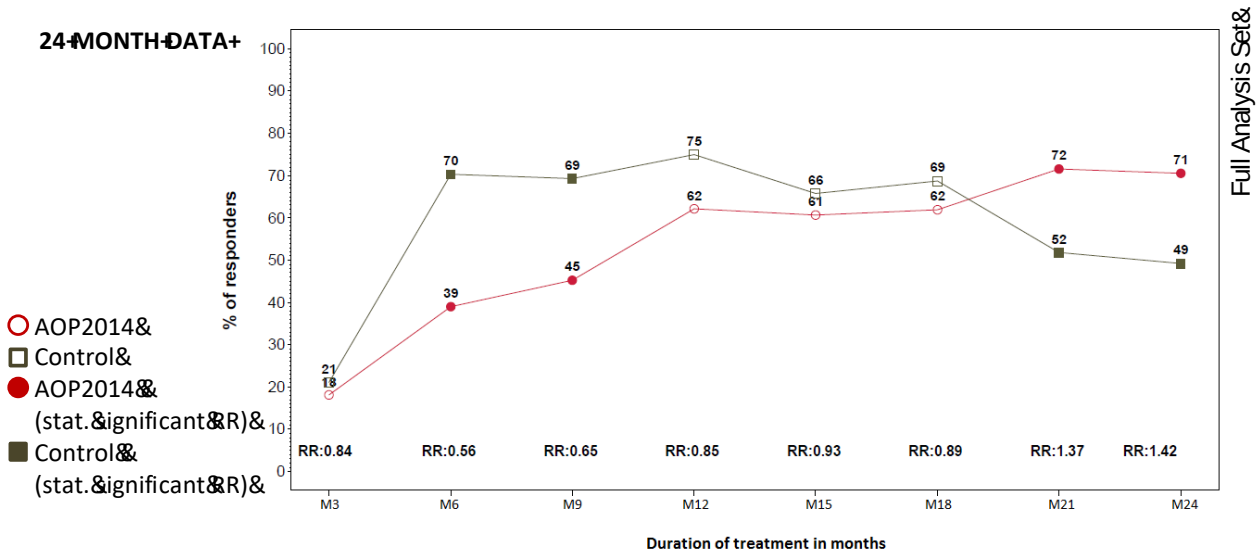
PROUD-PV: a *non-inferiority* randomized trial comparing HU with ropegIFN in *naive* and <3y-treated PV patients



Gisslinger et al, ASH 2017 Abstract Number: 320

PROUD-PV: Efficacy results

	AOP2014	Control	RR [95% CI] (AOP2014/Control)&	P-value
Complete Hematologic Response at&M24&	**70.5%** (67/95)&	**49.3%** (33/67)&	1.42&[1.09=1.87]&	0.0101&
CHR & Improvement in Disease Burden at& M24&	**49.5%** (47/95)&	**36.6%** (26/71)&	1.34&[0.93=1.92]&	0.1183&
Partial Molecular Response at&M24&(LOCF)&	**68.1%** (64/94)&	**34.7%** (26/75)&	1.85&[1.33=2.56]&	0.0002&



Gisslinger et al, ASH 2017, Abstract Number: 320

PROUD-PV: Adverse events of special interest

Long term Safety (up to 3.6 years of treatment; mean 2.7 years)	AOP2014 (n=127)	Control (n=127)
Endocrine disorders*	5 (3.9%)	1 (0.8%)
Psychiatric disorders**	3 (2.4%)	1 (0.8%)
Cardiac/Vascular disorders	13 (10.2%)	7 (5.5%)
Stroke	2 (1.6%)	0 (0.0%)
Thrombotic event	2 (1.6%)	2 (1.6%)
Cardiac failure	0 (0.0%)	2 (1.6%)
Atrial fibrillation	5 (3.9%)	3 (2.4%)
Others§	4 (3.2%)	0 (0.0%)
Tissue disorders***	2 (1.6%)	0 (0.0%)

* Autoimmune thyroiditis, Hypo-/Hyperthyroidism
** Anxiety, Depression, Mood altered
*** Rheumatoid arthritis, Sjogren's Syndrom
§ additional events reported: peripheral arterial occlusive disease (presented already in medical history), hematemesis, phlebitis

Long term Safety (up to 3.6 years of treatment; mean 2.7 years)	AOP 2014 (n=127)	Control (n=127)
Acute leukemia		2
Basal cell carcinoma		2
Malignant melanoma		1
Adrenal neoplasm*	1	
Glioblastoma	1	
Spermatocytic seminoma	1	

* No additional information on type of neoplasm available

Gisslinger et al, ASH 2017, Abstract Number: 320

Prediction of prognosis in PV after diagnosis

Bad factors:

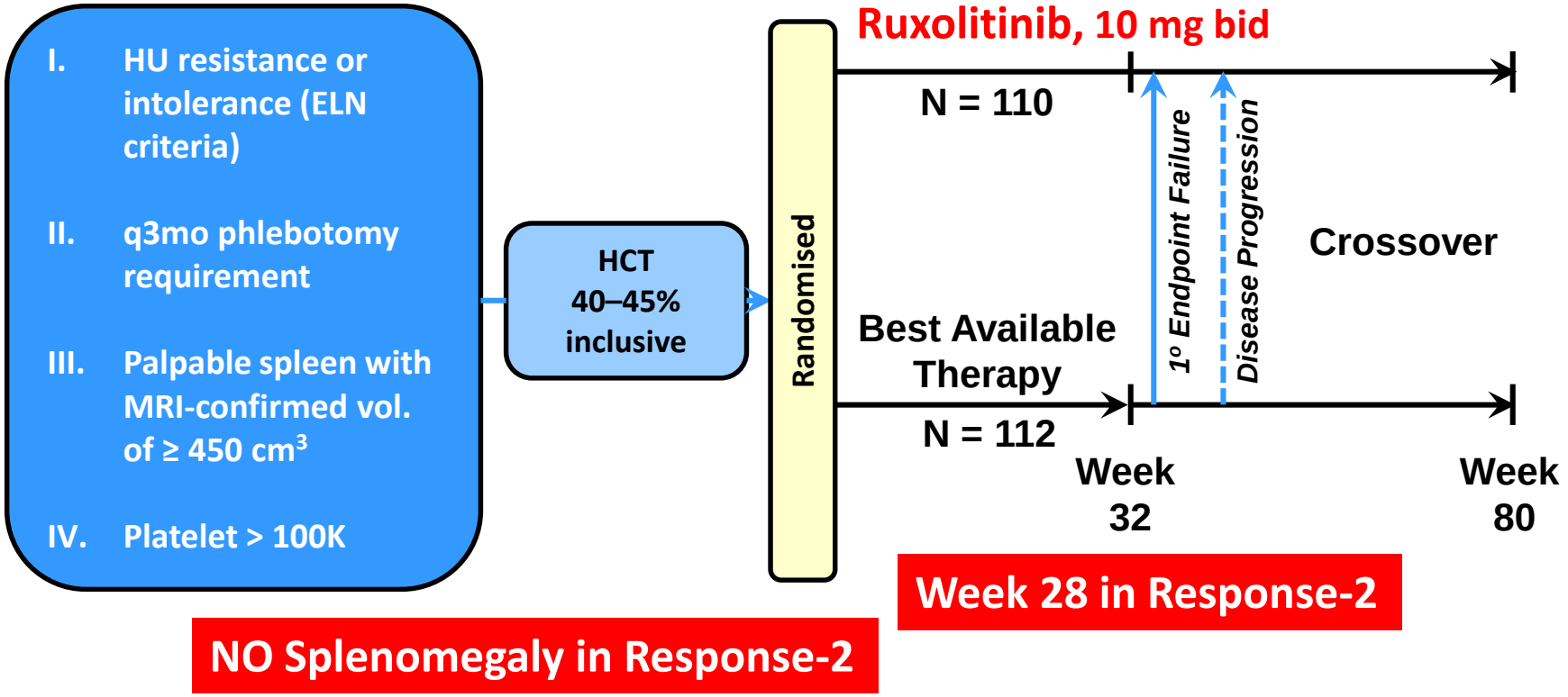
- Hematocrit values over 45%
- Inadequately controlled PV

Inadequately controlled PV
HU resistance & intolerance definition for studies
The size of the problem in 890 patients

- Recorded in 137 patients (15.4%):
  - Need for phlebotomies (3.3%)
  - Uncontrolled myeloproliferation (1.6%)
  - Failure to reduce massive splenomegaly (0.8%)
  - Cytopenia at the lowest HU-dose to achieve response (1.7%)
  - Extra-haematological toxicity (9%)
- **Cytopenia affected survival, progression to MF, AML**
- **Splenomegaly affected MF**

Alvarez-Larran et al; Br J Haematol. 2016 Mar;172(5):786-93

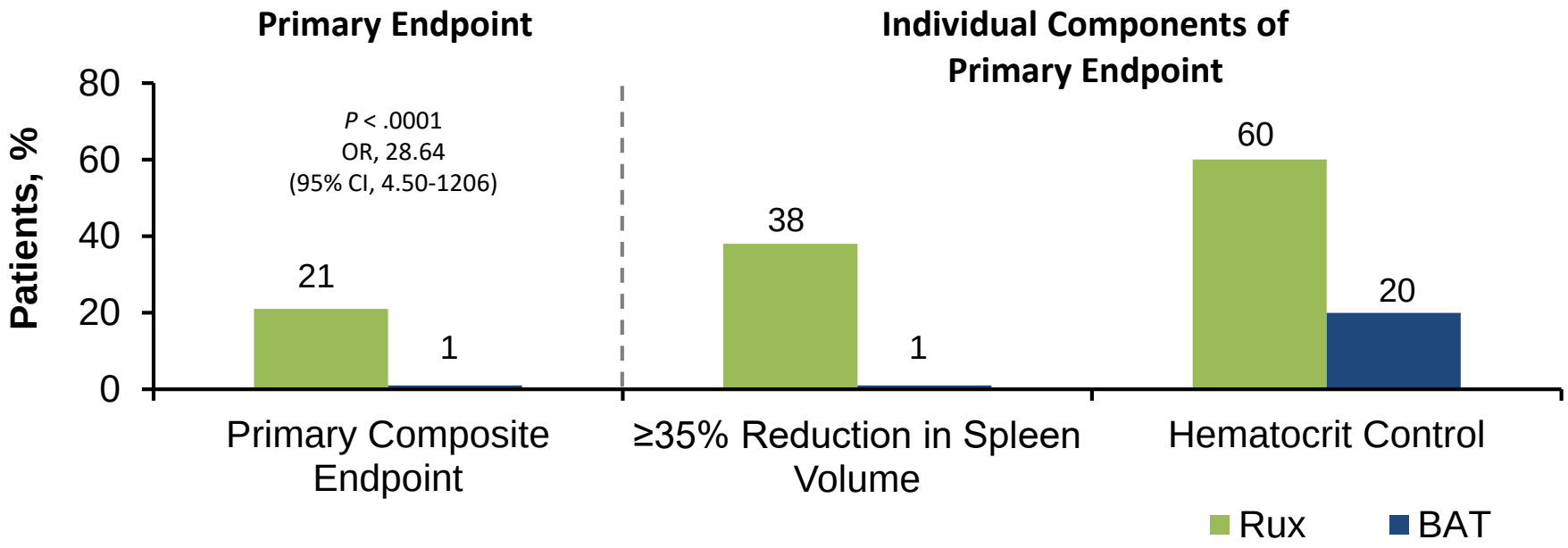
Ruxolitinib in PV: Phase 3 Trials *RESPONSE and RESPONSE 2*



- Primary composite endpoint: haematocrit control (phlebotomy independence from week 8 to 32, with ≤ 1 phlebotomy post randomization) in the absence of phlebotomy and 35% reduction in spleen volume at week 32 (this latter absent in Response 2)
- Secondary endpoints: complete haematological remission at week 32 (absence of phlebotomy requirement, PLT count ≤ 400 x 10^9/L, and WBC count ≤ 10 × 10^9/L); % of patients who maintain primary endpoint response for ≥ 48 weeks; Symptom improvement (MPN-SAF diary) and quality of life (EORTC QLQ-C30; PGIC).

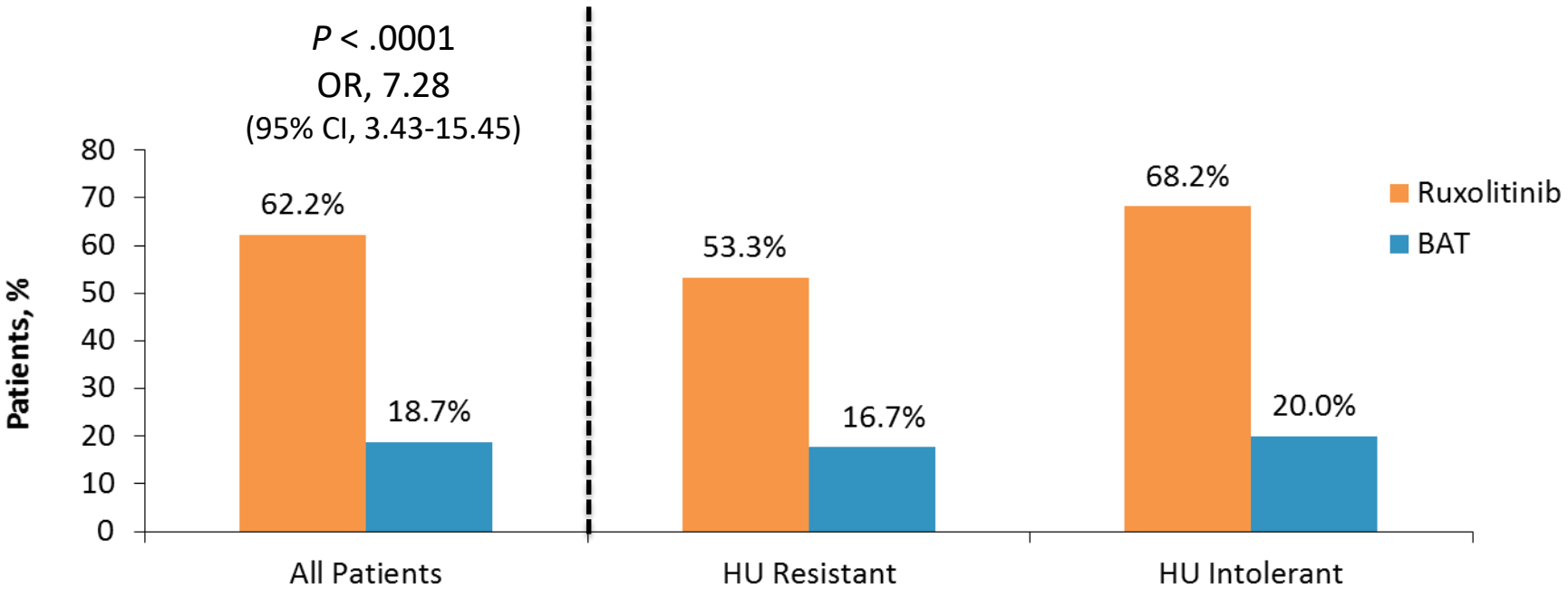
Vannucchi et al, N Engl J Med. 2015 Jan 29;372(5):426-35;
Passamonti et al, Lancet Oncol. 2016 Dec 1. pii: S1470-2045(16)30558-7.

RESPONSE study: haematocrit control and 35% reduction in spleen volume at Week 32



Vannucchi et al, N Engl J Med. 2015 Jan 29;372(5):426-35

RESPONSE-2 study: haematocrit control at Week 28

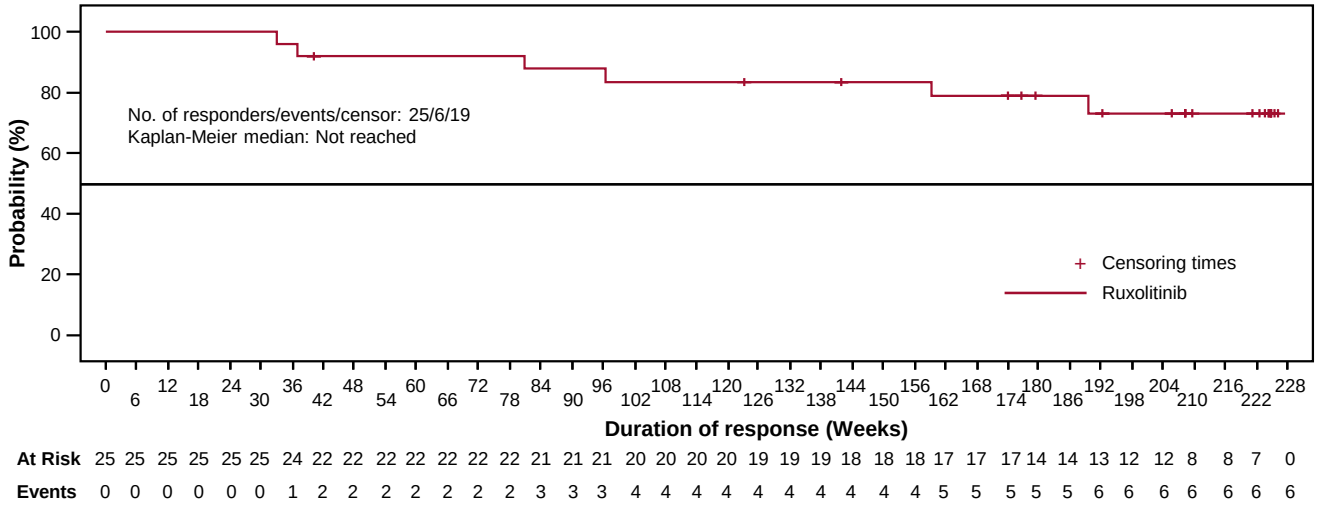


- Significantly more patients randomized to ruxolitinib achieved Hct control without phlebotomy (primary endpoint) compared with those randomized to BAT

OR, odds ratio.

Passamonti et al, Lancet Oncol. 2016 Dec 1. pii: S1470-2045(16)30558-7.

4-y RESPONSE trial: RUX durability of primary response



- The K-M estimate of duration of maintaining primary response for 208 weeks (4 years) was 0.73 (95% CI: 0.49, 0.87).
  - The K-M estimates of duration of hematocrit control for 208 weeks was 0.73 (95% CI: 0.60, 0.83).
  - The K-M estimates of duration of at least 35% reduction in the spleen volume was 0.86 (95% CI: 0.61, 0.95).
- Median duration of primary response has not been reached.

Kiladjian et al, Abstract Number: 322

4-y RESPONSE trial: other adverse events of interest

(Nonmelanoma Skin Cancer Adjusted for Patient-Year Exposure)

n (Rate per 100 Patient-Years of Exposure)	208-Week (4-Year) Analysis				80-Week Analysis			
	Ruxolitinib n = 110 Exposure, Patient-Years = 409		Crossover n = 98 Exposure, Patient-Years = 310		Ruxolitinib n = 110 Exposure, Patient-Years = 227.7		Crossover n = 98 Exposure, Patient-Years = 147.6	
Prior history of Nonmelanoma Skin Cancer	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Total events	**13 (3.6)**	**8 (18.6)**	**6 (2.1)**	**2 (9.5)**	**4 (2.0)**	**6 (24.2)**	**2 (1.4)**	**1 (10.6)**
Basal cell carcinoma	10 (2.7)	7 (16.3)	4 (1.4)	1 (4.7)	3 (1.5)	5 (20.2)	1 (0.7)	1 (10.6)
Squamous cell carcinoma of skin	4 (1.1)	4 (9.3)	3 (1.0)	0	1 (0.5)	2 (8.1)	0	0
Bowen's disease	1 (0.3)	1 (2.3)	0	0	0	1 (4.0)	0	0
Carcinoma in situ of skin	0	2 (4.7)	0	0	0	1 (4.0)	0	0
Metastatic squamous cell carcinoma	0	2 (4.7)	0	0	0	1 (4.0)	0	0
Keratoacanthoma	1 (0.3)	0	0	0	0	0	0	0
Squamous cell carcinoma*	2 (0.5)	3 (7.0)	2 (0.7)	2 (9.5)	1 (0.5)	4 (16.1)	1 (0.7)	0

Kiladjian et al, Abstract Number: 322

Conclusions

- Ruxolitinib is the standard new treatment for high risk MF with a 50% SVR representing the new bar of treatment goals in MF
- Fedratinib, pacritinib, momelotinib are under investigation and will enter market soon
- JAKi-based combination trial are under investigation hoping to extend clinical/molecular activity
- Peg-Interferon or hydroxyurea are for first line high risk PV, while ruxolitinib is the current second-line treatment in PV