Ruxolitinib in polycythemia vera

Alessandro M. Vannucchi

CRIMM- Center Research and Innovation of MPN

University of Florence, Italy

UNIVERSITÀ DEGLI STUDI FIRENZE

Azienda Ospedaliero Universitaria Careggi

Second-Line Treatment for PV

Low Risk

- Frequent need of PHL and poor tolerance
- Symptomatic or progressive splenomegaly
- Progressive (symptomatic) thrombocytosis
- Progressive leukocytosis
- Progressive disease-related symptoms

Thrombosis -score

High Risk

- Aspirin (81-100mg/d)[1, @]
- Hydroxyurea[3] *or* Interferon [§ 4]
- ±Phlebotomy to HCT<45%[2]

Resistance

Intolerance

- **Ruxolitinib[#]**
- Hydroxyurea
- Interferon [§]
- Busulfan*
- Clinical trial

[@], anticoagulants in case of venous thrombosis. [§], off-label; could be considered for younger patients.
[#], approved indication. Approved for reimbursement in Italy Dec 2017. * for older subjects.

*Barbui T et al, 2011; JCO 29:761. 2017; submitted. Vannucchi AM et al, 2015; Ann Oncol; 26:v85. NCCN Guidelines v2.2018. [1]Landolfi R et al, 2004; *NEJM*. 350:114. [2]Marchioli R et al, NEJM;2013;368:22. [3]Fruchtman SM et al, Sem Hematol 1997;34:17. [4], Gisslinger H et al, ASH2016.

Resistance or Intolerance to Hydroxyurea in PV

RESISTANCE	Hydroxyurea
• Need of phlebotomy to maintain Hct <45%	After 3 months of ≥2 g/day HU
• PLT >400x10^9/L and WBC >10x10^9/L	
• Spleen reduction by <50% *or* • No complete relief of spleen-related symptoms	
INTOLERANCE	
• ANC <10^9/L *or* • PLT <100x10^9/L *or* • Hb <100g/L	• At the lowest dose to achieve hematologic response
• Leg ulcers *or* • Other unacceptable HU-related toxicities*	• At any dose of HU

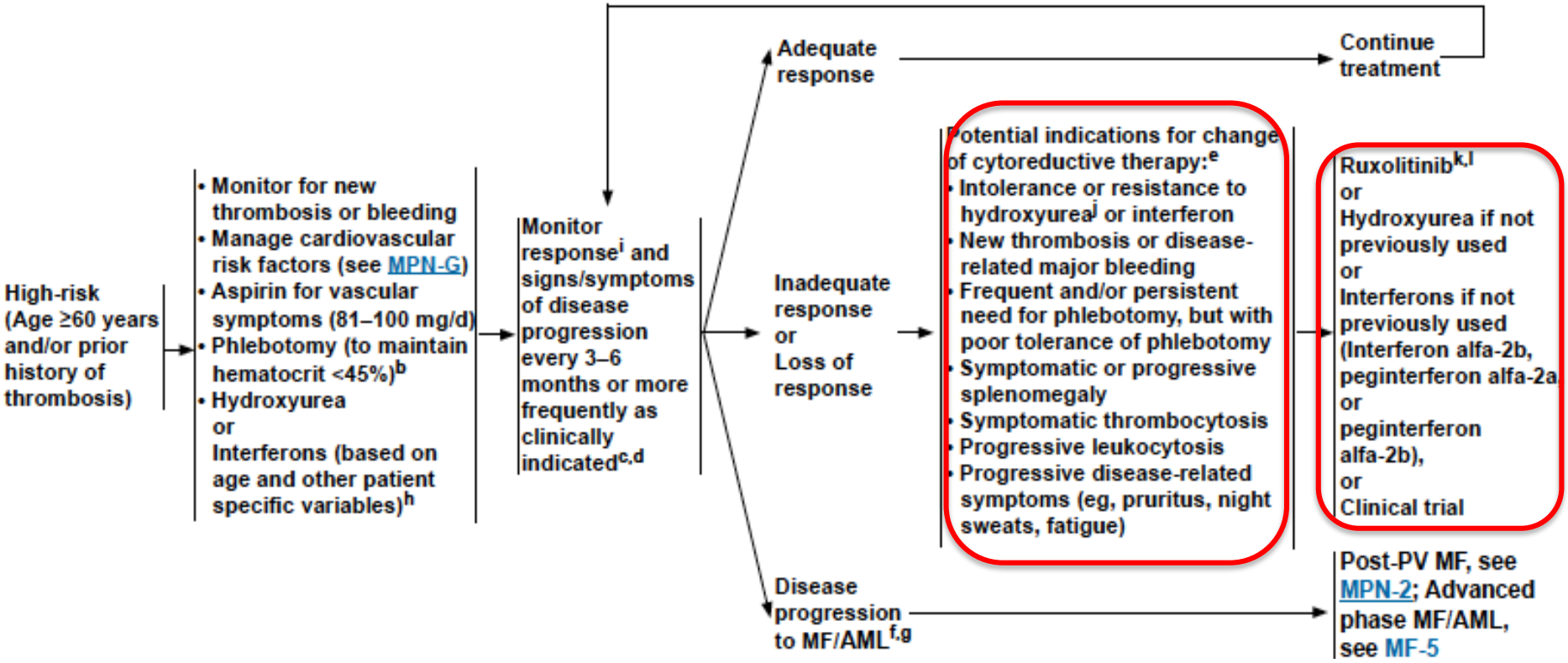
- Rate of discontinuation of HU in PV patients was 11% for resistance and 13% for refractoriness

NB: these definitions were developed for clinical trials, not for clinical practice.

*Mucocutaneous, gastrointestinal, pneumonitis, fever

1. Barosi G, et al. Br J Haematol. 2010;148(6):961. 2 Alvarez-Larrán *et al*, Blood 2012;119(6):1363. 3. Alvarez-Larrán *et al*, BJH 2016;172(5):786. 4. Barbui T et al, Haematologica 2017; 102:e219.

TREATMENT FOR HIGH-RISK POLYCYTHEMIA VERA



Revised Management Recommendations from European LeukemiaNet

- The Panel agreed that both rIFNa and ruxolitinib are appropriate second-line drug therapies for PV patients who are intolerant or have inadequate response to hydroxyurea.

- In this setting, the recommendation of use of ruxolitinib was judged as strong , even though the confidence in outcome measures was moderate.

- In the absence of a direct comparison of the two agents, the choice should be based on the patient's age and drug availability.

- rINFa should be preferred in young patients in need of long-term treatment.

RESPONSE: Prospective Trials of PV patients with Resistance/Refractoriness to Hydroxyurea

- Resistance to or intolerance of HU (modified ELN criteria)
- Phlebotomy requirement
- Splenomegaly (spleen volume ≥450 cm³)

- **Resistance to or intolerance of HU (modified ELN criteria)**
- **Phlebotomy requirement**
- **No palpable spleen**

Pre-randomization (day −28 to day −1) Hct 40% to 45%

Randomized 1:1

Ruxolitinib 10 mg twice daily
n=110

Week 28

Extended treatment phase

Week 256

n=74

Week 32 (primary endpoint)

Week 48 (primary data cutoff)

Week 80 (planned analysis)

Week 256

Crossover to ruxolitinib

BAT
n=112

n=75

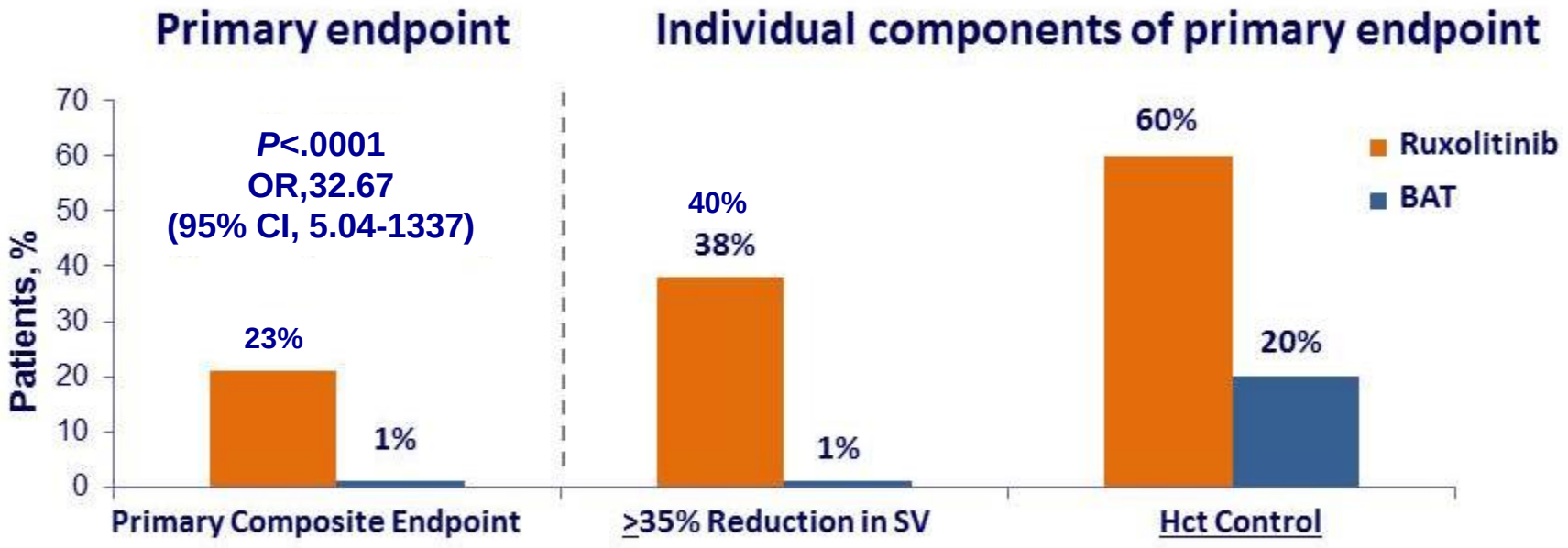
- Investigator-selected BAT as monotherapy included HU (at a tolerated dose if the patient were likely to receive benefit), interferon (IFN)/peg-IFN, anagrelide, pipobroman, immunomodulatory drugs, or observation
- All patients received low-dose aspirin unless medically contraindicated

- Patients randomized to BAT were allowed to cross over to ruxolitinib at W32 (28) if they did not meet the primary endpoint or after W32 (28) in case of phlebotomy eligibility or splenomegaly progression (RESPONSE only)

Vannucchi AM et al, NEJM 2015; 372:426; Passamonti F et al, Lancet Oncol 2017;18:88-98.

RESPONSE: Primary Endpoint of the Study

- **Primary endpoint (composite):** Percentage of patients who achieved both Hct control (Hct <45% and no phlebotomy) and spleen response (reduction of SV to ≤35% from baseline assessed by MRI) at week 32.

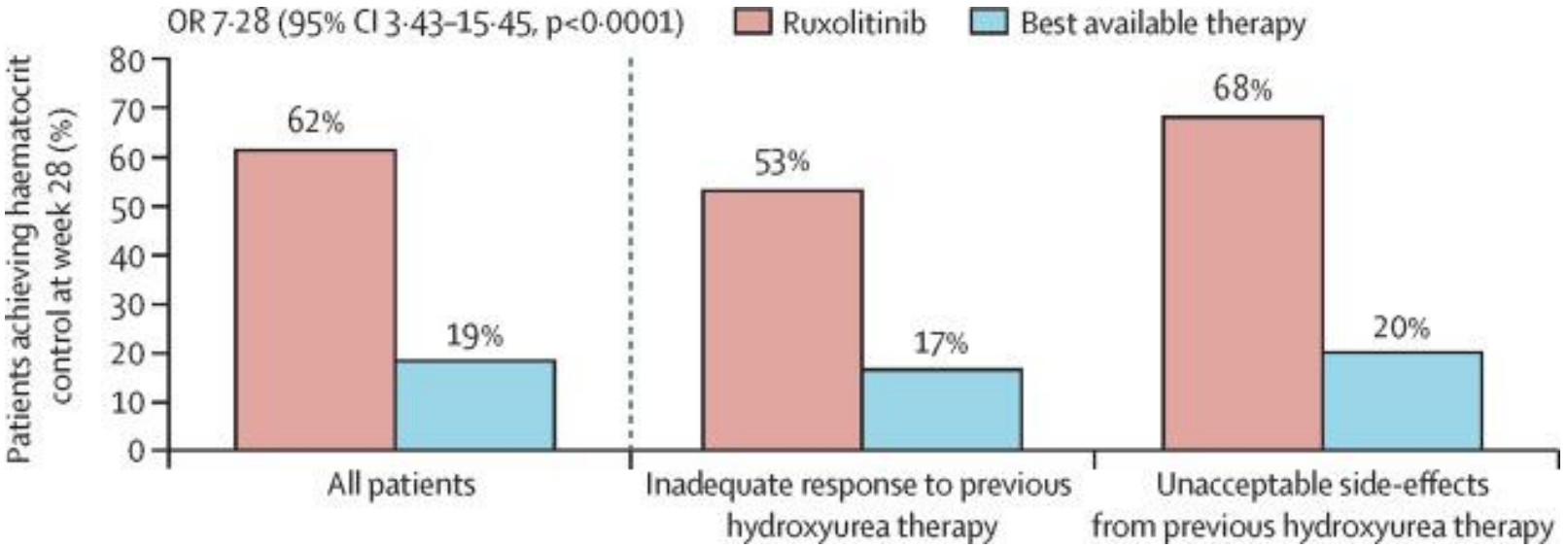


- 77% of patients randomized to ruxolitinib met at least 1 component of the primary endpoint

Vannucchi AM et al, NEJM 2015; 372:426

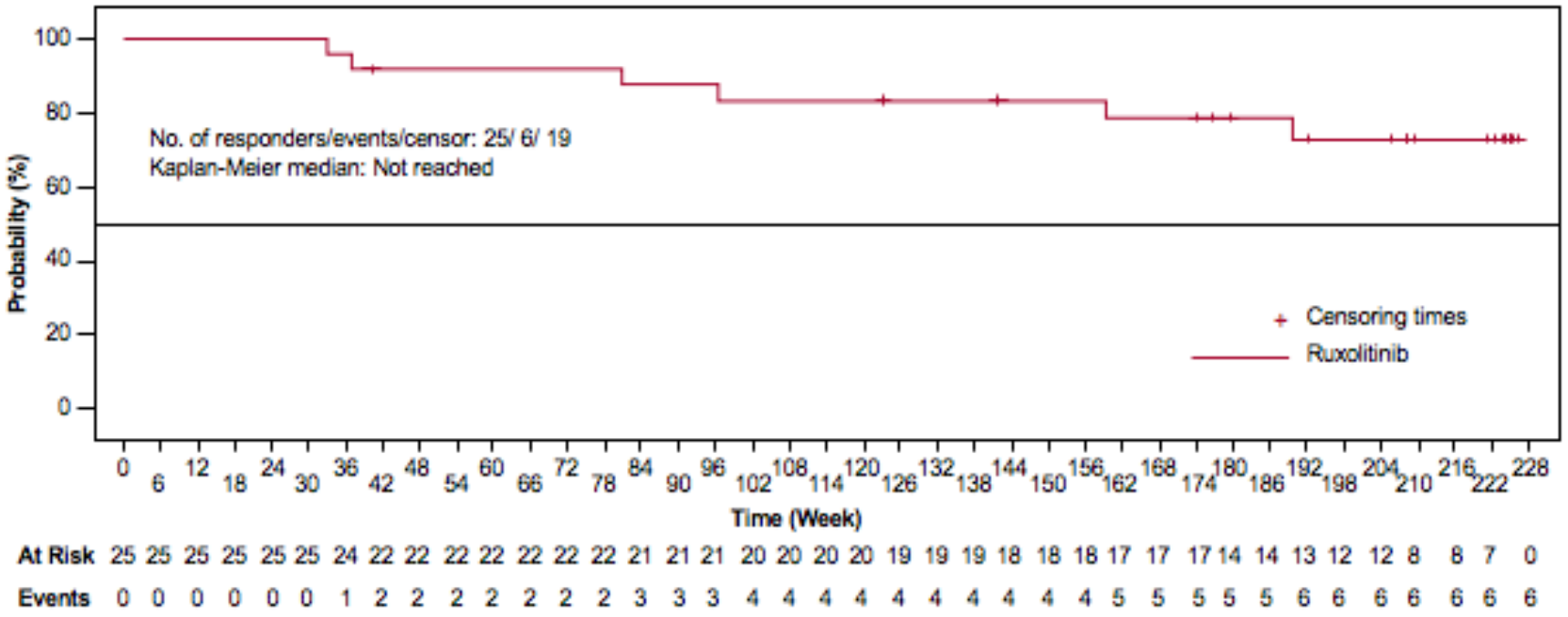
RESPONSE-2: Primary Endpoint of the Study

- Hematocrit control



Passamonti F et al, Lancet Oncol 2017; 18:88-98

Durability of Primary Response With Ruxolitinib



- At the time of analysis in the ruxolitinib arm, 6 of 25 primary responders have progressed.
- 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.**

CI, confidence interval; K-M, Kaplan–Meier.

JJ Kiladjian, ASH 2017

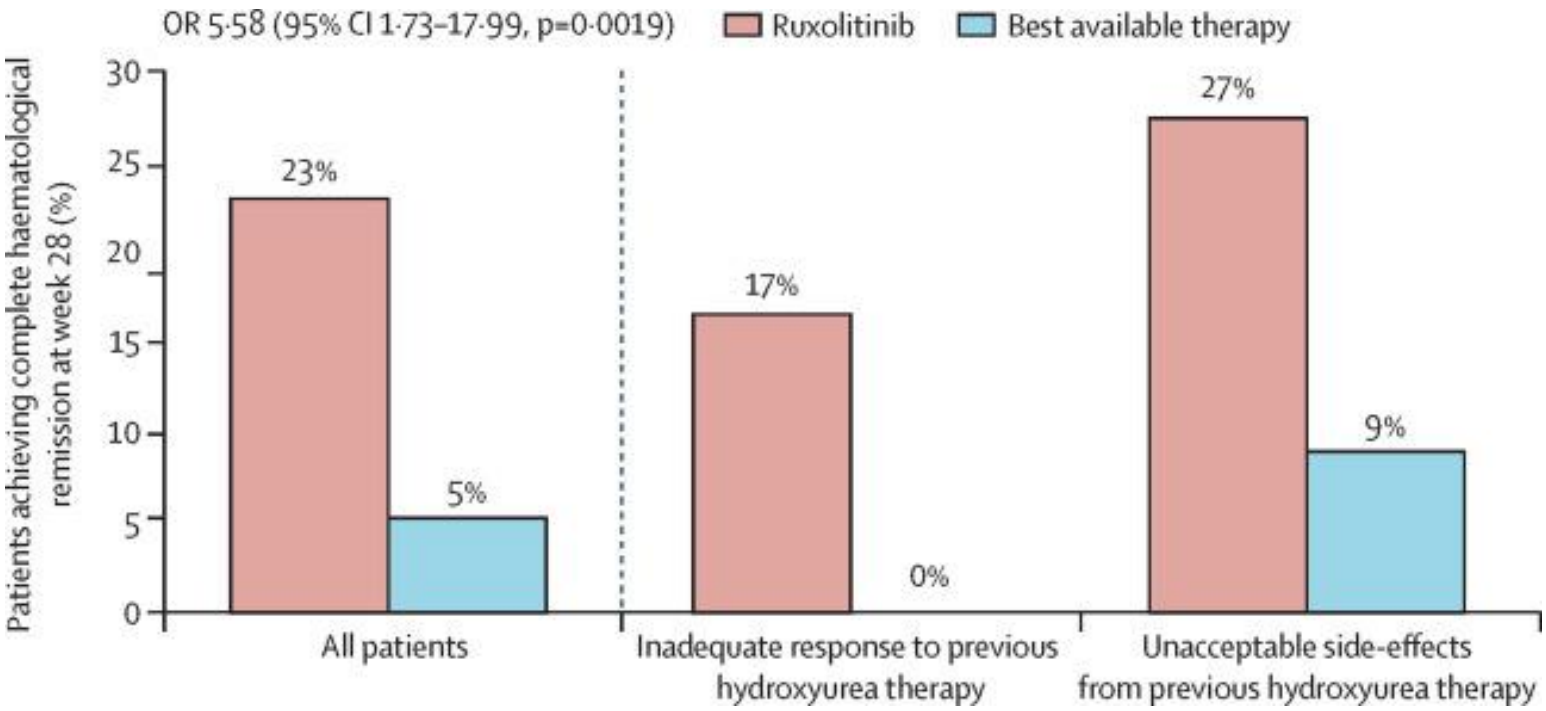
Sustained Control of Blood Cell Counts in Patients Receiving Ruxolitinib in RESPONSE

Changes in WBC Counts and Platelet Counts in Ruxolitinib Arm	N	Week 32 % Patients	Week 80 % Patients
WBC ≤10 x 10^9/L in patients with baseline WBC >10 x 10^9/L	87	31.0	47.1
WBC ≤10 x 10^9/L in patients with baseline WBC >15 x 10^9/L	64	26.6	42.2
Platelets ≤400 x 10^9/L in patients with baseline platelet count >400 x 10^9/L	54	44.4	59.3

- **The probability of maintaining CHR for ≥80 weeks from time of response was 69%**
- Percentage of patients with normalized WBC and platelet counts **improved over time with ruxolitinib treatment**

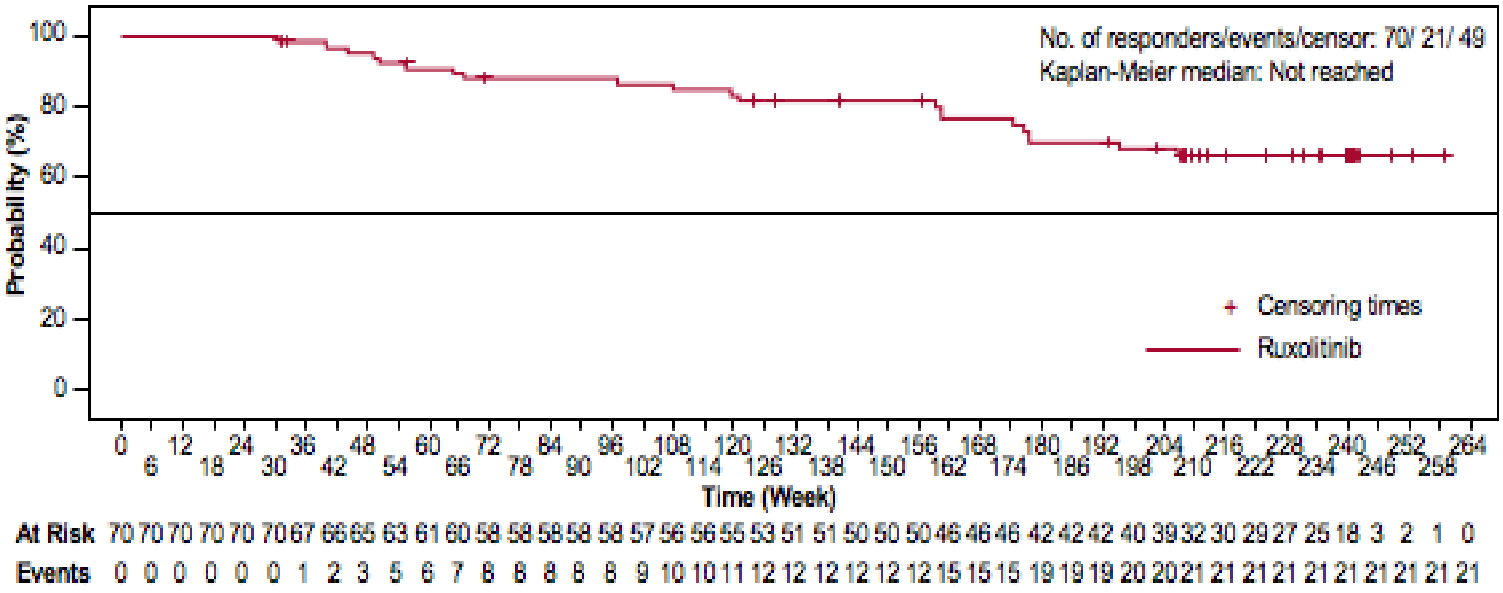
Verstovsek S. et al. Haematologica 2016;101:821-829

RESPONSE-2: Complete Hematologic Response



Passamonti F et al, Lancet Oncol 2017; 18:88-98

Durability of Complete Hematologic Remission With Ruxolitinib

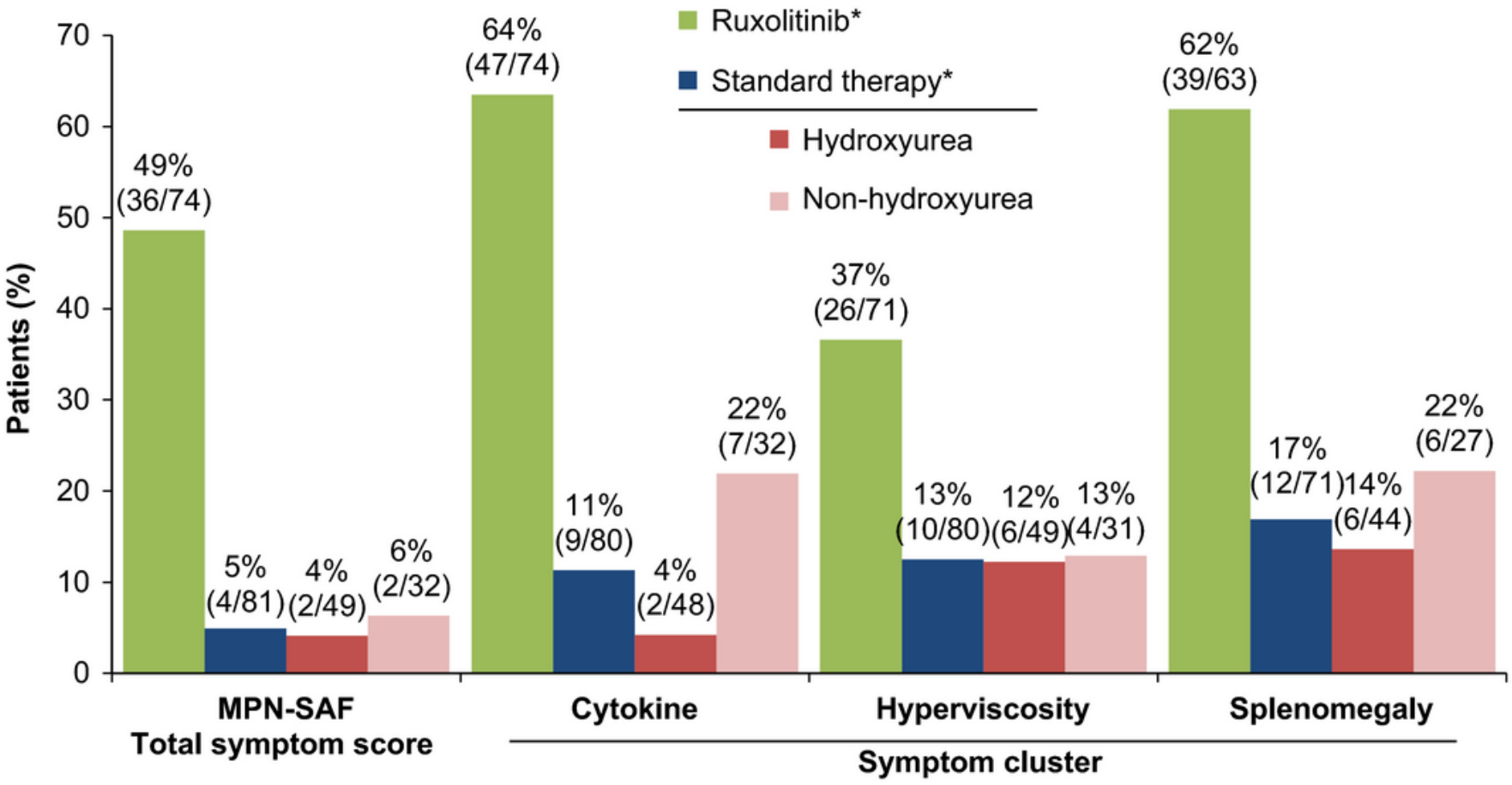


- The **K-M estimate of duration of CHR** (hematocrit control, platelet count ≤ 400 × 10^9/L, and WBC count ≤ 10 × 10^9/L) **for 208 weeks (4 years) was 0.54** (95% CI: 0.31, 0.72).
  - Of 87 patients with WBC > 10 ×10^9/L at baseline, 42 (48.3%) achieved WBC ≤ 10 × 10^9/L at week 208.
  - Of 54 patients with platelet count > 400 × 10^9/L at baseline, 26 (48.1%) achieved platelet count ≤ 400 × 10^9/L at week 208 .

CHR, complete hematologic remission; CI, confidence interval; K-M, Kaplan-Meier

JJ Kiladjian, ASH 2017

Disease-related Symptoms in Patients with PV Receiving Ruxolitinib or Standard Therapy



Vannucchi AM et al, NEJM 2015; 372:426-35.

Thromboembolic Adverse Events

(Adjusted for Patient-Year Exposure, Regardless of Study Drug Relationship [All Grades, Rate ≥ 0.2 in Either Arm])

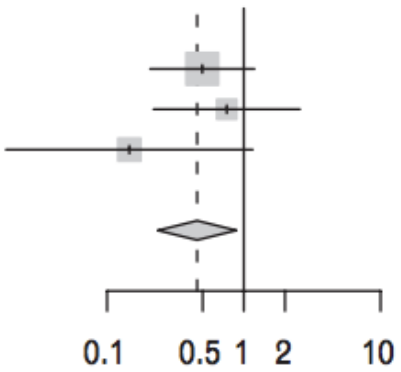
	208-Week (4-Year) Analysis				80-Week Analysis			
	Ruxolitinib n = 110 Exposure, Patient-Years = 409		Crossover n = 98 Exposure, Patient-Years = 310		Ruxolitinib n = 110 Exposure, Patient-Years = 227.7		Crossover n = 98 Exposure, Patient-Years = 147.6	
n (Rate per 100 Patient-Years of Exposure)	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
All thromoboembolic events[a]	**5 (1.2)**	**3 (0.7)**	**9 (2.9)**	**5 (1.6)**	**4 (1.8)**	**2 (0.9)**	**6 (4.1)**	**4 (2.7)**
Cerebral infarction	1 (0.2)	1 (0.2)	0	0	1 (0.4)	1 (0.4)	0	0
Ischemic stroke	1 (0.2)	0	1 (0.3)	1 (0.3)	1 (0.4)	0	0	0
Transient ischemic attack	0	0	2 (0.6)	2 (0.6)	0	0	2 (1.4)	2 (1.4)
Portal vein thrombosis	1 (0.2)	1 (0.2)	0	0	1 (0.4)	1 (0.4)	0	0
Pulmonary embolism	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Retinal vascular thrombosis	1 (0.2)	0	0	0	1 (0.4)	0	0	0
Myocardial infarction	0	0	2 (0.6)	1 (0.3)	0	0	2 (1.4)	1 (0.7)
Deep vein thrombosis	0	0	1 (0.3)	0	0	0	0	0
Thrombophlebitis	0	0	1 (0.3)	0	0	0	0	0
Thrombosis	0	0	1 (0.3)	0	0	0	1 (0.7)	0
Bone infarction	0	0	1 (0.3)	0	0	0	1 (0.7)	0
Coronary artery occlusion	0	0	1 (0.3)	0	0	0	1 (0.7)	0
Disseminated intravascular coagulation	0	0	1 (0.3)	1 (0.3)	0	0	1 (0.7)	1 (0.7)

- While on BAT, the rates of all grade and grade 3/4 thromboembolic events per 100 patient-years of exposure were 8.2 (n = 6) and 2.7 (n = 2), respectively.

Meta-Analysis of Thromboembolic Events in Trials of Ruxolitinib in MPN Patients

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	W(fixed)
COMFORT1 2012	7	155	14	154	0.50	[0.21; 1.20]	53.4%
COMFORT2 2012	6	146	4	73	0.75	[0.22; 2.58]	20.3%
RESPONSE 2015	1	110	7	112	0.15	[0.02; 1.16]	26.4%
Fixed effect model		411		339	0.46	[0.23; 0.88]	100%

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = 0.4018$



- Observed for arterial and venous events also when considered separate.

Samuelson BT et al, J Coag Fibr 2014; 27:648-52.

Adverse Events Associated with Ruxolitinib

Exposure, Patient-Years	Ruxolitinib (n=110) 227.7 n (exp adjusted rate)	BAT (n=111*) 73.6 n (exp adjusted rate)
All infections	67 (29.4)	43 (58.4)
Grade 3 or 4	9 (4.0)	3 (4.1)
Herpes zoster infection	12 (5.3)	0
Grade 3 or 4	2 (0.9)	0
Nonmelanoma skin cancer†	10 (4.4)	2 (2.7)
Patients with a history of NMSC	6 (24.2)	1 (22.3)
Patients without a history of NMSC	4 (2.0)	1 (1.4)
Disease progression‡		
Myelofibrosis	3 (1.3)	1 (1.4)
AML	1 (0.4)	0

*1 patient was randomized to BAT but did not receive study treatment

†There were 3 additional events of NMSC after crossover, 1 in a patient with a history of skin cancer or precancer
Patients with history of NMSC: n=12, 24.8 pt-yrs exposure in ruxolitinib arm; n=7, 4.5 pt-yrs exposure in BAT arm
Patients without a history of NMSC: n=98, 202.9 pt-yrs exposure in ruxolitinib arm, n=104, 69.1 pt-yrs exposure in BAT arm

‡ There was 1 additional report of myelofibrosis in the ruxolitinib arm, but this was not confirmed with bone marrow biopsy; there were 3 cases of myelofibrosis in the BAT arm after crossover to ruxolitinib; 1 of these patients developed AML

Good hematologic tolerability: Anemia G>3=0.9%, Thr'penia G>3 2.6%, Neutropenia G>3 0.4%, Lymphopenia G>39.7%

Verstovsek S et al. Haematologica 2016; 101:821-6.

Adverse Events

(Adjusted for Patient-Year Exposure, Regardless of Study Drug Relationship [All Grades, Rate ≥ 5 in Either Arm])

	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	
Rate per 100 Patient-Years of Exposure	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Hematologic adverse events								
Anemia	**9.3**	**1.0**	**9.4**	**0.6**	**13.2**	**0.9**	**14.9**	**1.4**
Thrombocytopenia	**4.6**	**1.0**	**1.3**	**0.3**	**6.1**	**1.8**	**2.7**	**0.7**
Non-hematologic adverse events								
All infections	19.6	3.7	19.7	6.5	29.4	4.0	27.8	5.4
Herpes zoster infection	**4.9**	**0.5**	**4.2**	**0.6**	**5.3**	**0.9**	**5.4**	**0.7**
Pruritus	7.3	0.5	5.8	0	9.7	0.4	8.8	0
Diarrhea	7.1	0.2	3.2	0	9.7	0	5.4	0
Headache	6.1	0.5	5.5	0	10.5	0.9	8.8	0
Fatigue	5.1	0.2	4.2	0	8.3	0.4	6.8	0
Increased weight	5.6	0.7	4.2	0.3	7.5	0.4	6.8	0
Arthralgia	5.9	0.2	3.2	0.3	6.1	0	4.7	0
Muscle spasms	5.4	0.2	3.2	0	7.9	0.4	3.4	0
Dizziness	4.2	0.0	6.1	0	7.5	0	7.5	0

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 NMSC	**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

*Categorized as non-skin squamous cell carcinoma cases.

Other Adverse Events of Interest

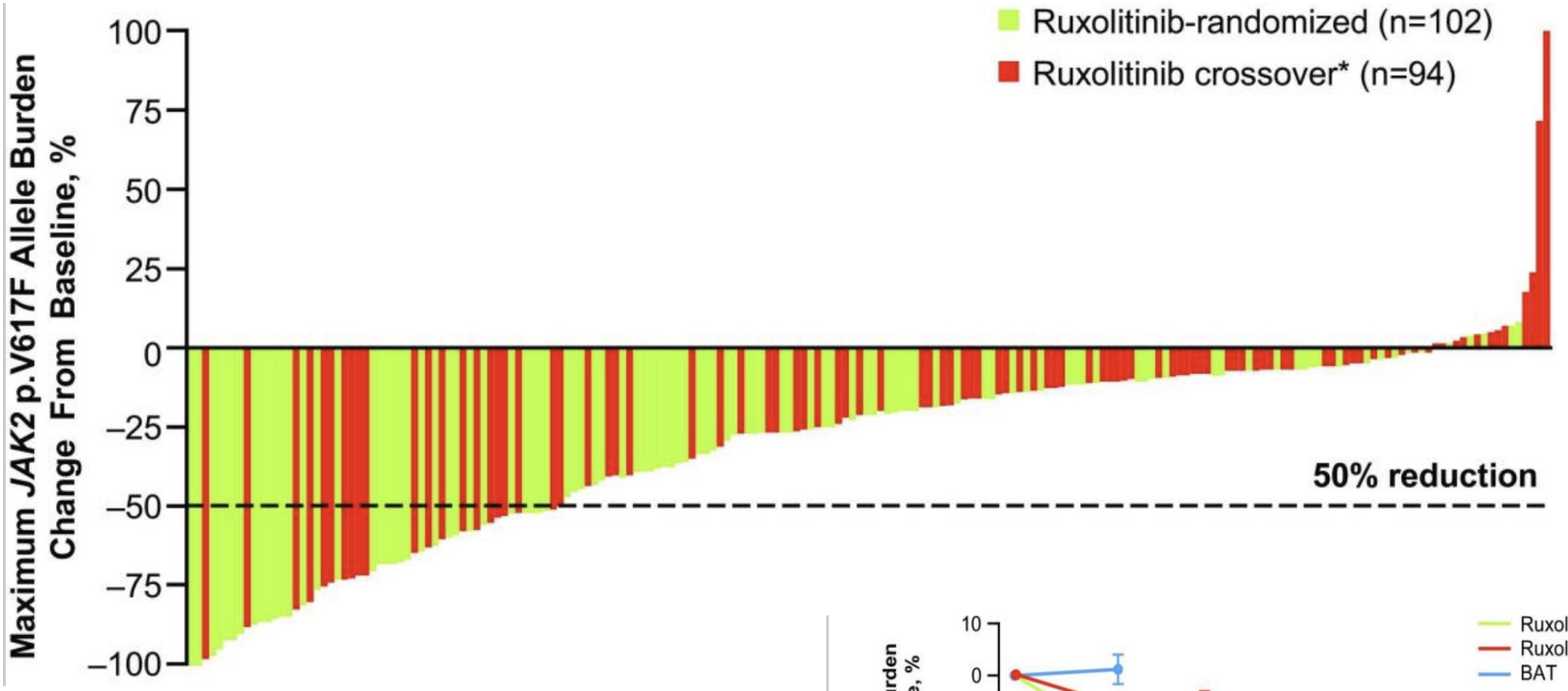
(Adjusted for Patient-Year Exposure, Regardless of Study Drug Relationship [All Grades, Rate ≥ 0.5 in Either Arm])

	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
	n (Rates)	n (Rates)	n (Rates)	n (Rates)
Disease Progression				
Acute myeloid leukemia	1 (0.2)	1 (0.3)	1 (0.4)	1 (0.7)
Myelofibrosis	9 (2.2)	6 (1.9)	3 (1.3)	3 (2.0)
Other Malignancies				
Prostate cancer	1 (0.2)	2 (0.6)	0	2 (1.4)
Breast cancer	2 (0.5)	0	2 (0.9)	0
Chronic myelomonocytic leukemia	1 (0.2)	1 (0.3)	0	1 (0.7)
Malignant fibrous histiocytoma	0	0	0	1 (0.7)

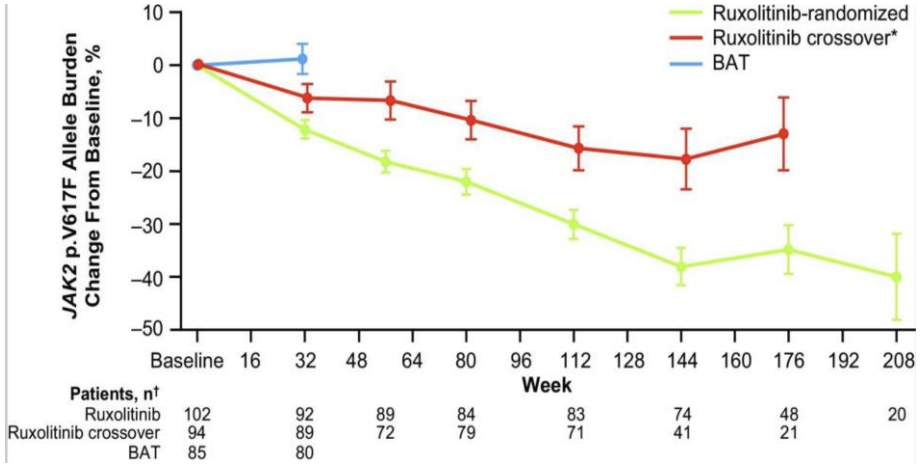
BAT; best available therapy.

- While on BAT, no patient progressed to acute myeloid leukemia or myelofibrosis.

*JAK2*V617F VAF Changes in the RESPONSE Trial



- The mean (SD) maximal reductions in allele burden in ruxo--randomized and crossover arms were **–35.9%** (29.7%) and **–21.2%** (30.7%).
- The median times to maximal reduction of alleleburden were burden were **25.9 and 18.2 months**.



Vannucchi AM et al, AOHE, 2017; 96:1113-20

Conclusions

- Ruxolitinib is an effective, well tolerated, second line drug for managament of patients with PV who are refractory or resistant to hydroxyurea

- Left unmet clinical needs:
  - Safety signals, particularly skin cancers in previously heavily treated patients and with previous history of NMSC
  - Will ruxolitinib induce molecular remissions in the long-term?
  - How to provide indisputable evidence about reduction of thrombosis?
  - Economical impact, for very long-term use