Ruxolitinib: criteri di resistenza, indicazioni, gestione della terapia, effetti collaterali

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ELN definition of clinico-hematologic response in PV

Response grade	Response in PV
Complete response	1. Hematocrit <45% **without** phlebotomy, ***and*** 2. Platelet count ≤400 × 10^9/L, ***and*** 3. WBC count ≤10 × 10^9/L, ***and*** 4. Normal spleen size on imaging, ***and*** 5. No disease-related symptoms[a]
Partial response	1. Hematocrit <45% without phlebotomy, ***or*** 2. Response in ≥3 of the other criteria
No response	Any response that does not satisfy partial response

[a]Disease-related symptoms include microvascular disturbances, pruritus, and headache
WBC, white blood cell count

Barbui T, et al. *J Clin Oncol*. 2011(6);29:761-770.

Rate of hematologic responses to HU in PV

261 PV patients (median follow-up, 7.2 years) treated with HU for a median of 4.4 years at a single center.

Complete hematological response	24%
Partial hematological response	66%
No response	10%

- Achieving complete or partial response or hematocrit response did not result in better survival or less thrombosis and bleeding.
- Having no response in WBC was associated with higher risk of death (HR, 2.7, p=0.007)
- Lack of response in PLT was associated with higher risk of thrombosis and bleeding

Alvarez-Larrán *et al*, Blood 2012;119(6):1363-9

ELN Criteria for Hydroxyurea Resistance and Intolerance in PV

Intolerance/Resistance

- Need for phlebotomy (to Hct <45%)
- Platelets > 400 x 10^9/L and WBC > 10 x 10^9/L
- No reduction of spleen by 50%
- No reduction of spleen symptoms

→ After > 3 mos at MTD or 2 g/day

- Cytopenias (any)
  - ANC < 1.0 x 10^9/L
  - Hemoglobin x 10^9/L
  - Platelets < 100 x 10^9/L

→ At lowest dose to achieve either a PR or CR

- GI toxicity
- Fever
- Mucocutaneous toxicity
- Skin cancers

→ At any dose

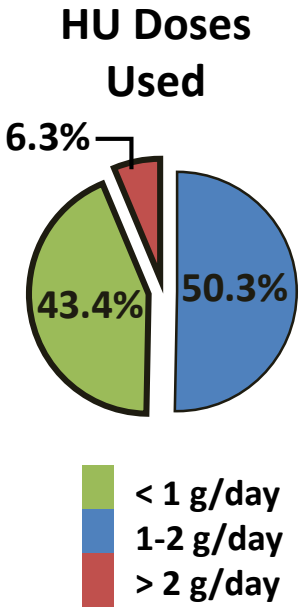
Barosi G et al. Br J Haematol. 2010;148:961-963.

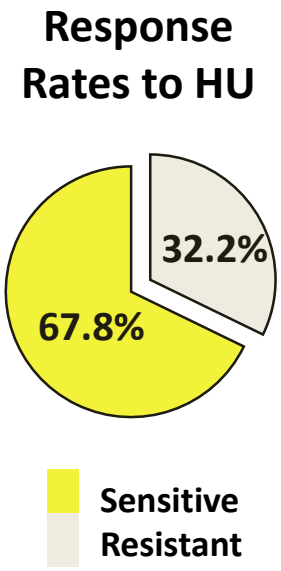
Characteristics and Treatment of PV with HU in clinical practice

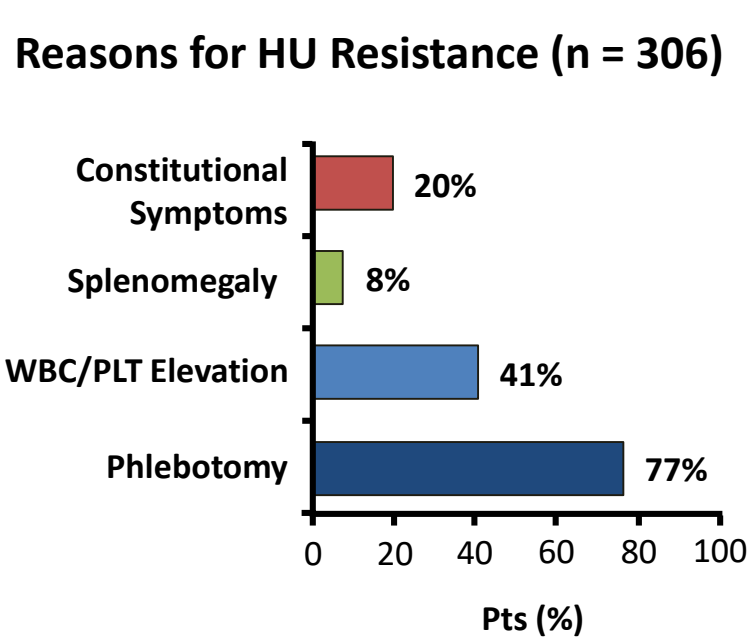
- A ‘real-life’ study in a cohort of **1467 patients** treated at 34 private practices and primary care centers in Germany.
- Most patients were of **older age** (66.7 % older than 66 years)
- Molecular status at diagnosis was not evaluated in 23% (diagnosed before 2008).
- Low rates of constitutional symptoms were reported: mostly concentration problems, fatigue and itching.
- **Phlebotomy and HU** were the main measures for Hct control.
- Interferon and JAK inhibitor therapy were used in **<10%** of patients, respectively.

Jentsch-Ullrich K, et al. J Cancer Res Clin Oncol. 2016;142:2041-2049.

Characteristics and Treatment of PV with HU in clinical practice







Jentsch-Ullrich K, et al. J Cancer Res Clin Oncol. 2016;142:2041-2049.

Management of PV in the “real life” – the experience of Udine

Variables	**All patients (n= 105)**
Phlebotomies	104 (99%)
Mean phlebotomies / year	4.26/year (n=100)
HU therapy	**86 (81.9%)**
Mean HU dose	**0.75 g/day**
CR to HU (according to ELN)	**24/86 (28%)**
Median FU	11.8 years (0.3 – 30.8)
Thrombosis [art. / ven.]	19 (18%) [12 (11%) / 7 (7%)]
Major hemorrhages (grade 3-4)	6 (5.7%)
Evolution in MF	10 (9.5%)
Deaths	6 (5.7%)

Discontinuation of HU in PV – real life data

Clinical significance of resistance and intolerance to HU in a series of **890 patients with PV** treated in Spain

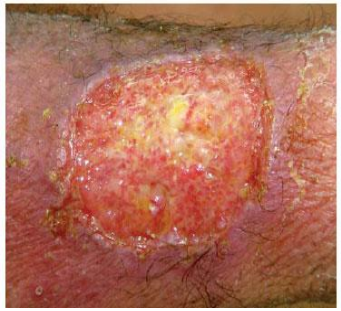
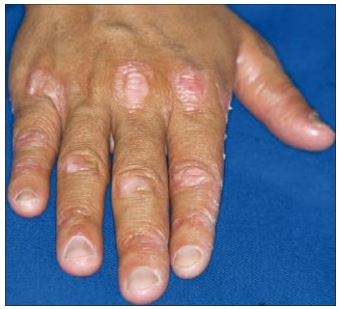
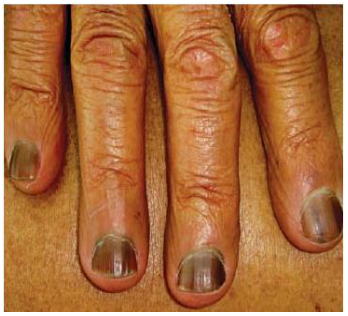
Res./intol. to HU was recorded in **137 patients (15.4%)**:

- need for phlebotomies = 3.3%
- uncontrolled myeloproliferation = 1.6%
- failure to reduce massive splenomegaly = 0.8%
- development of cytopenia at the lowest dose of HU to achieve a response = 1.7%
- extra-haematological toxicity = 9%

Alvarez-Larrán *et al*, Br J Haematol 2016;172:786-93

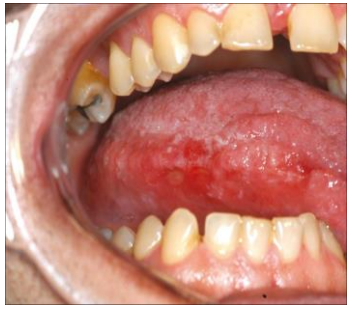
HU common side effects

Cutaneous:
malleolar ulcers
skin de- or hyper-pigmentation
nail changes
alopecia

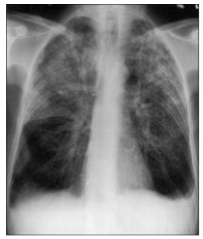
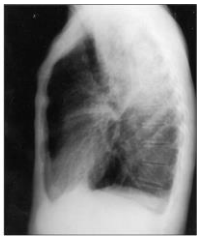
Lesions can appear right after the beginning of as a late effect; not associated with low ANC

Gastrointestinal:
nausea and vomiting
diarrhea
anorexia
glossitis and stomatitis

Fever

Pneumonitis (interstitial)

Resistance or intolerance to HU in the real life represent a therapeutic challenge

Busulfan	Potentially leukemogenic in long term treatment. Recommended in age over 75 years
Pipobroman	Potentially leukemogenic in long term treatment; withdrawn from the market. DO NOT USE
Radiophosphorus	Not recommended
IFN-α	Recommended in young patients Off label.
JAK2-inhibitors	Ruxolitinib

Cytoreductive options in PV patients according to ELN and ESMO recommendations

	First-line therapy		Second-line therapy	
	ELN	ESMO	ELN	ESMO
Hydroxyurea	+[1]	+	+	+
Interferon-α	+*	+*	+*	+*
Busulphan	+[2]		+[3]	+
Pipobroman, ^{32}P			+[4]	
Anagrelide	–	–	–	–
Ruxolitinib				+[5]

[1] use with caution in patiens <40 years
[2] >70 years
[3] for patients with short life expectancy
[4] not frequently used
[5] for resistant/refractory to hydroxycarbamide
*** off-label indication in Europe**

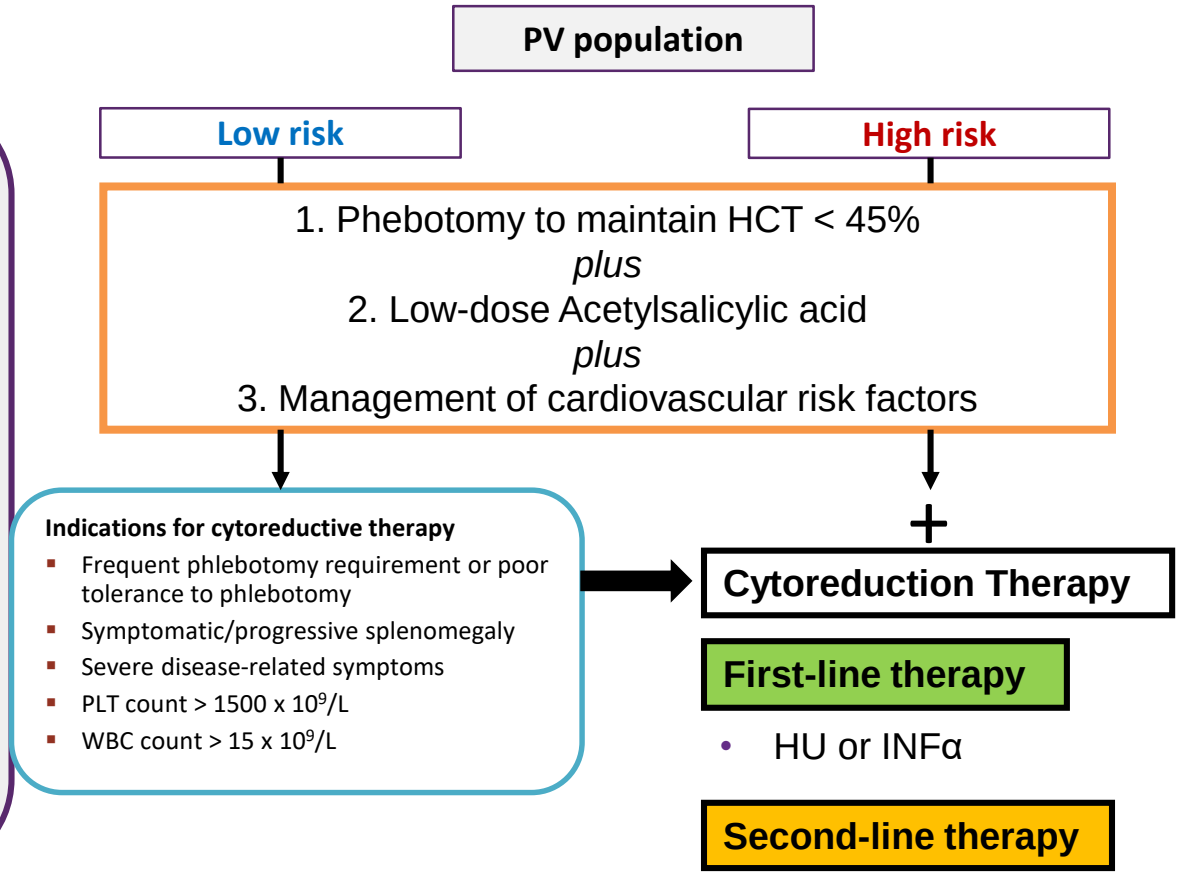
Barbui *et al*, J Clin Oncol 2011;29:761.
Vannucchi AM *et al*, Ann Oncol 2015;26

Treatment Strategy for PV: 2018 ELN recommendations

Therapy for patients with PV is determined by their prognostic risk

- **Low-risk** patients:
  Age < 60 years **AND**
  no history of thrombosis
- **High-risk** patients:
  Age ≥ 60 years **OR**
  with history of thrombosis

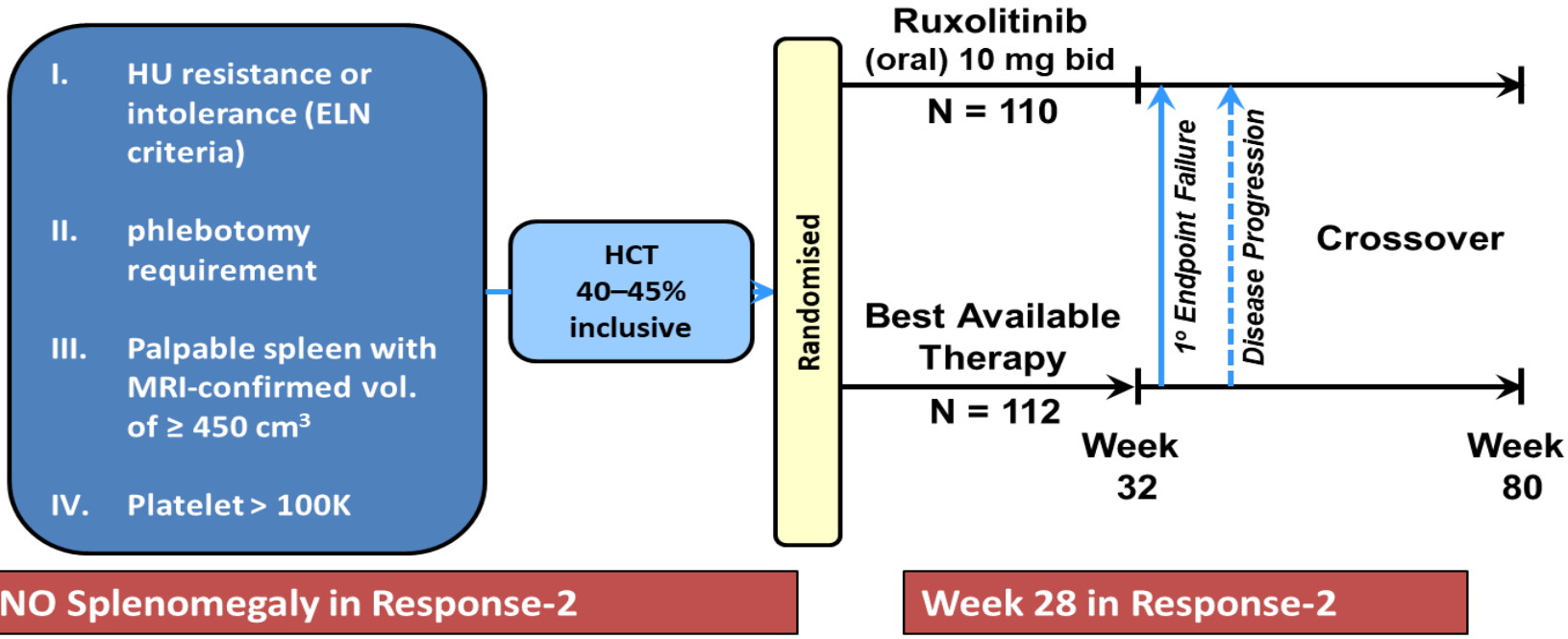
HCT should be maintained strictly at <45%



[a] Choice based on patient's age and drug availability.
[b] Preferred in young patients who need long-term treatment.

Barbui T, et al. J Clin Oncol. 2011;29:761-770
Barbui T, et al. Leukemia. 2018;32(5):1057-1069.

RESPONSE & RESPONSE-2 study design

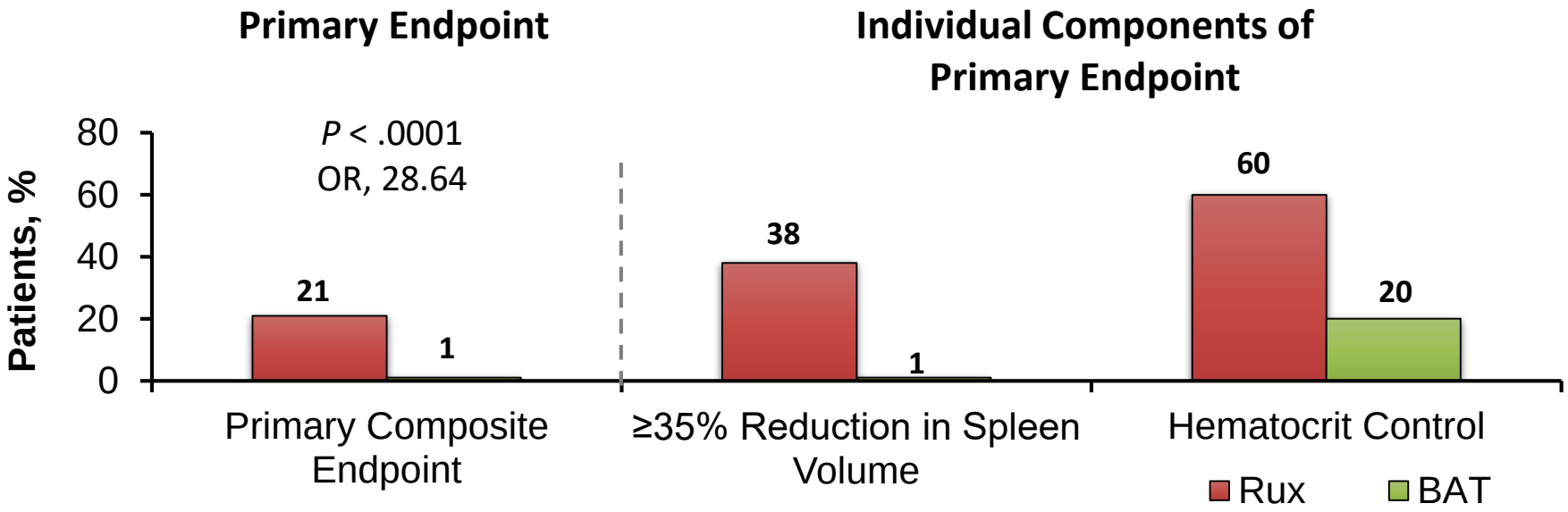


Primary composite endpoint: haematocrit control (phlebotomy independence from week 8 to 32, with ≤ 1 phlebotomy post randomization) in the absence of phlebotomy and 35% reduction in spleen volume at week 32 (this latter absent in Response 2)

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.

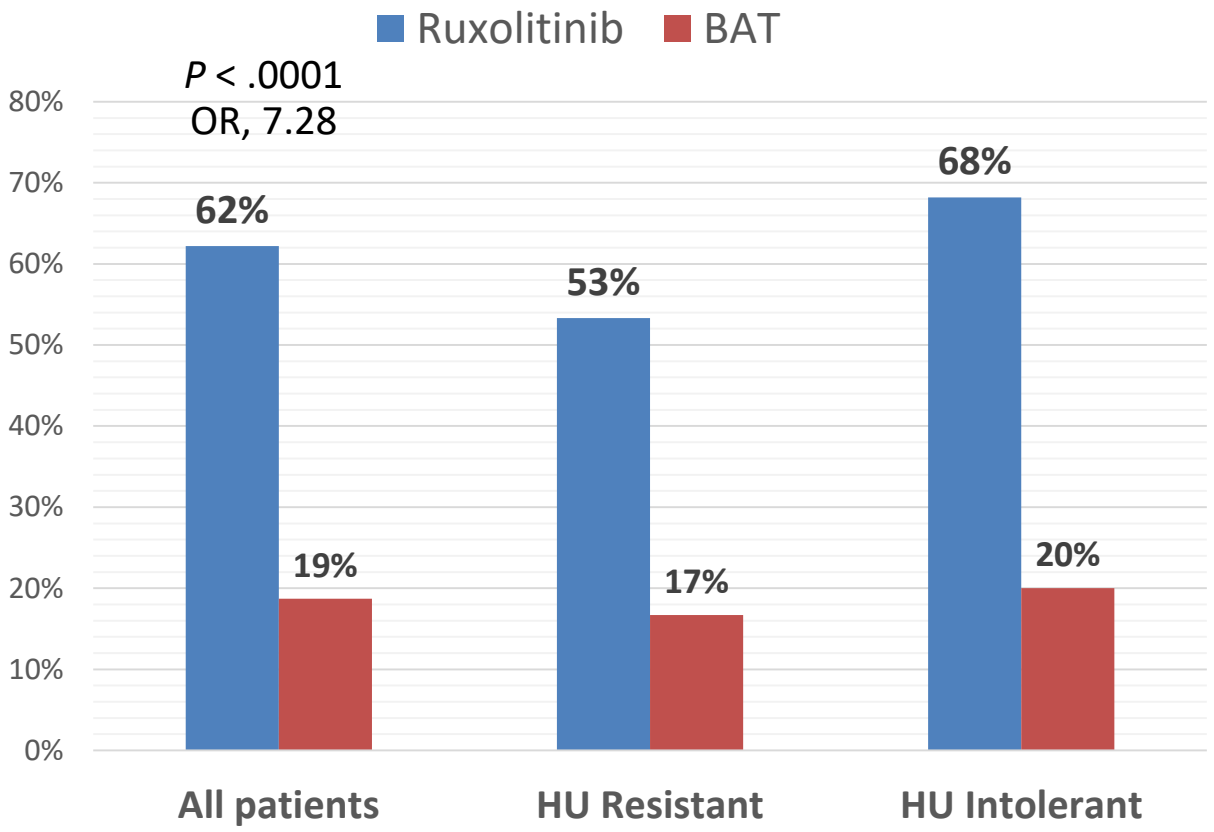
RESPONSE study – week 32 analysis
Hct control and spleen volume reduction



- 222 phlebotomy-dependent PV patients **with splenomegaly**, were randomized in a 1:1 ratio, to receive ruxolitinib (110 pts) or standard therapy (112 pts).
- **Patients randomized to RUX achieved higher rates of Hct control and spleen reductions**

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

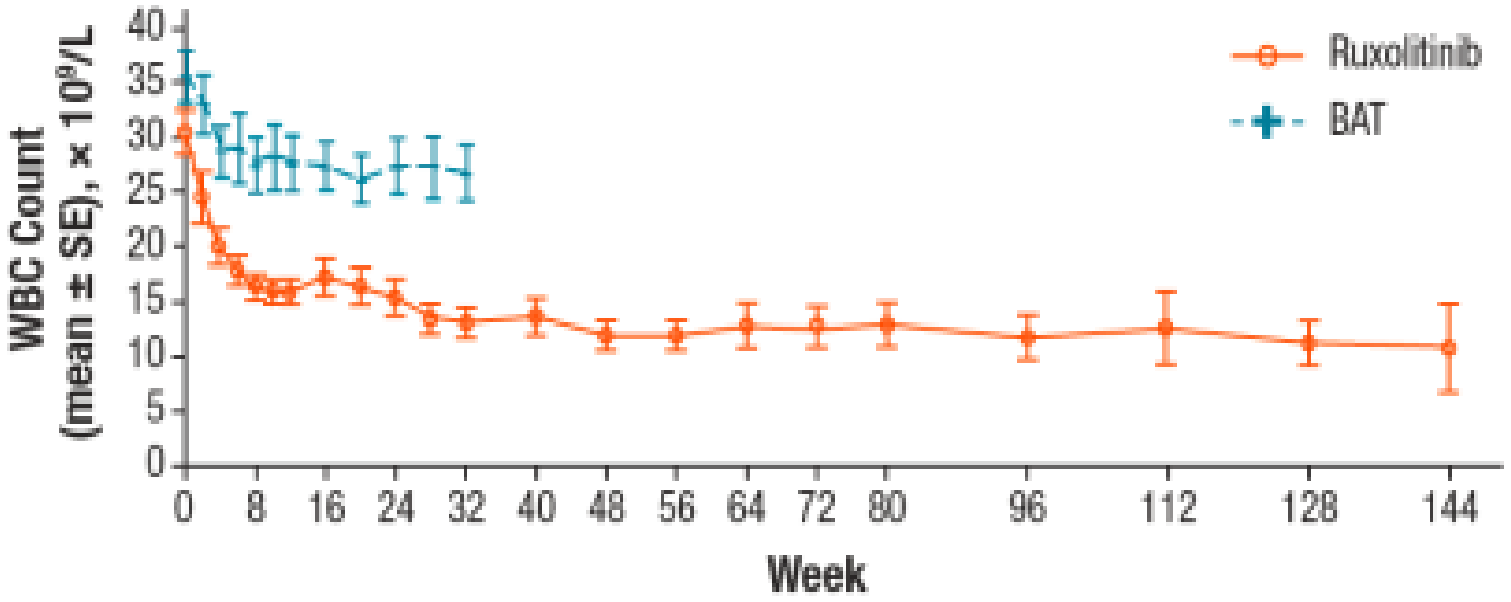
RESPONSE 2 study – week 28 analysis
Hct control



Significantly more patients randomized to ruxolitinib achieved Hct control without phlebotomy compared with those randomized to BAT

Passamonti F, et al. Lancet Oncol. 2017;18(1):88-99

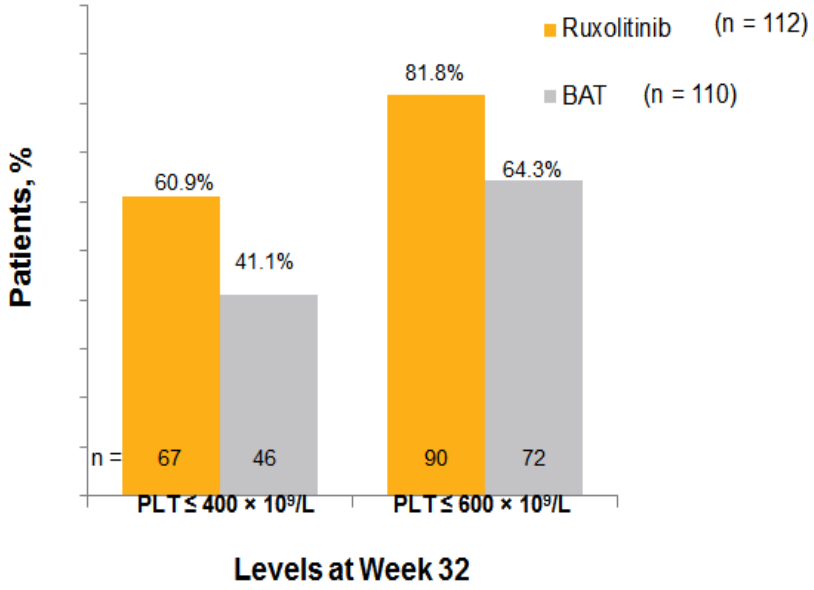
Ruxolitinib improves WBC count

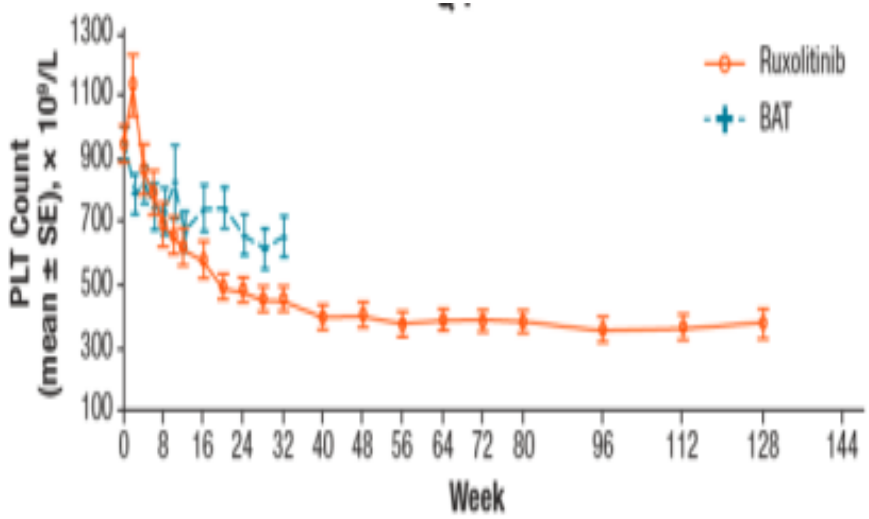


Patients with the highest WBC counts at baseline had the largest reductions, with mean values in the ruxolitinib arm of approximately 15 × 109/L or lower from week 8 onward (BAT arm remained > 25 × 109/L)

Harrison EHA 2015 EP1353;

Ruxolitinib improves PLT count





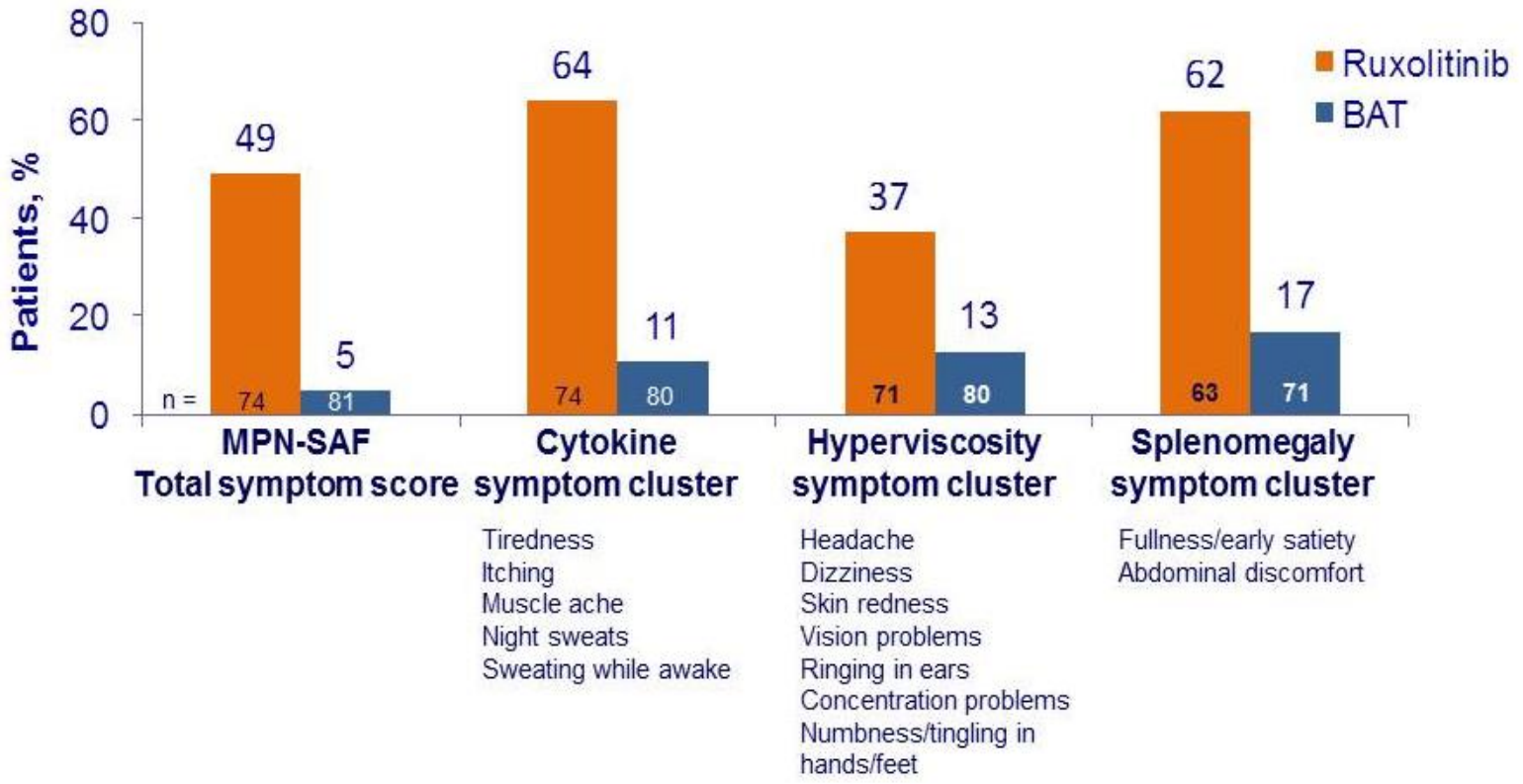
In comparison with BAT-treated patients, a **higher proportion of ruxolitinib-treated** patients had a PLT count ≤ 400 × 109/L at week 32 **(60.9% vs 41.1%);** a **higher proportion of patients randomized to ruxolitinib** had a PLT count ≤ 600 × 109/L at week 32 (81.8% vs 64.3%)

Patients with the highest PLT counts at baseline had the largest reductions, with mean values in the ruxolitinib arm of < 500 × 109/L from week 20 onward

Harrison EHA 2015 EP1353;

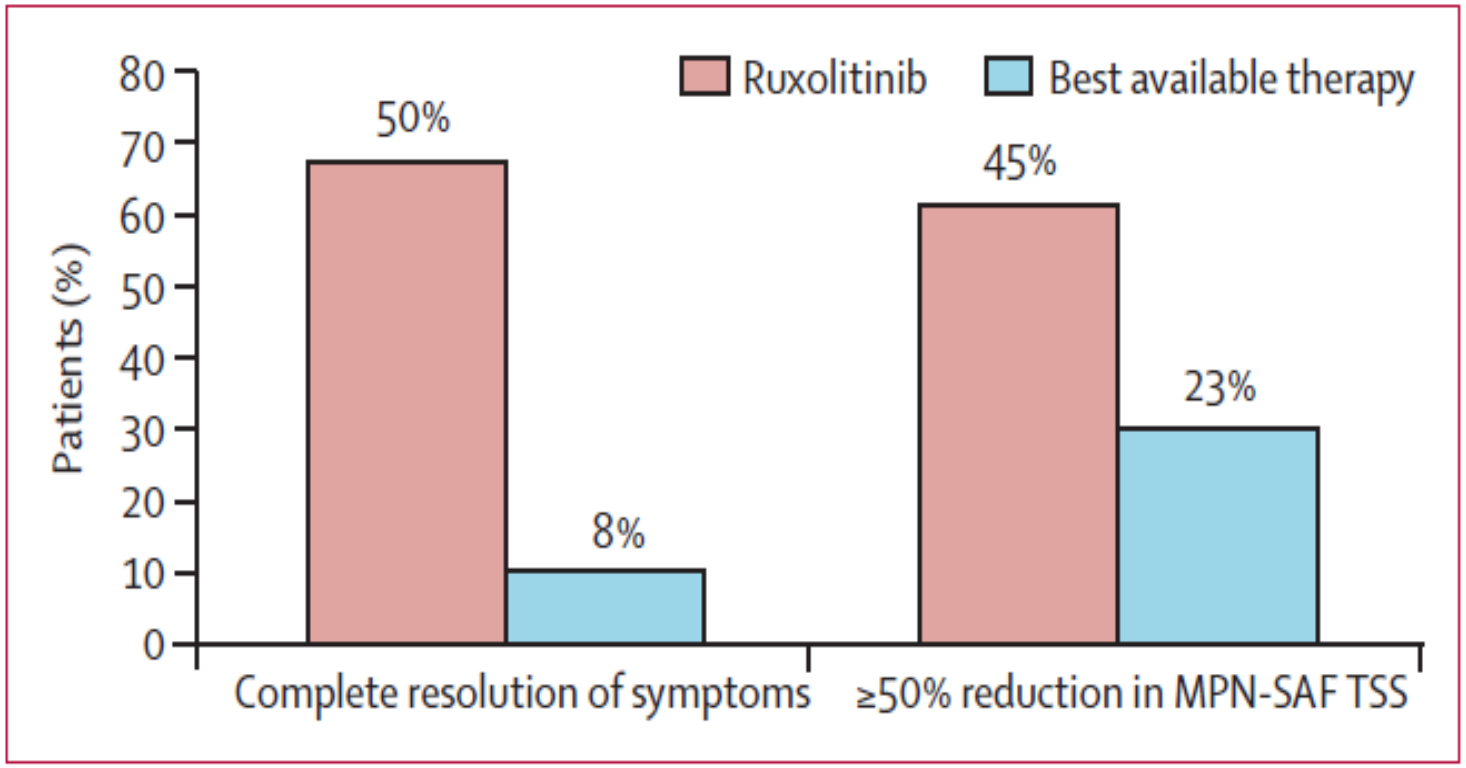
RESPONSE study – week 32 analysis
Symptoms response

- **Percentage of patients with a ≥50% improvement in MPN-SAF symptom score at week 32[a]**



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

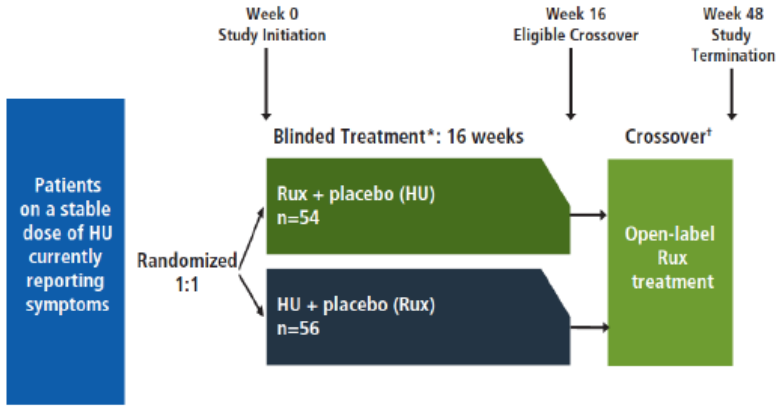
RESPONSE 2 study – week 28 analysis
Symptoms response

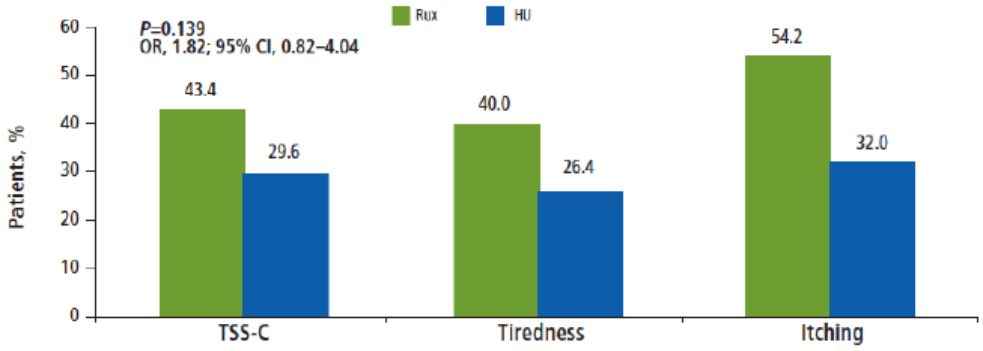


Patients achieving complete resolution of PV-related symptoms and ≥50% reduction in MPN-SAF TSS

Passamonti F, et al. Lancet Oncol. 2017;18(1):88-99

The RELIEF study





PV patients controlled on stable dose of HC but reported symptoms.

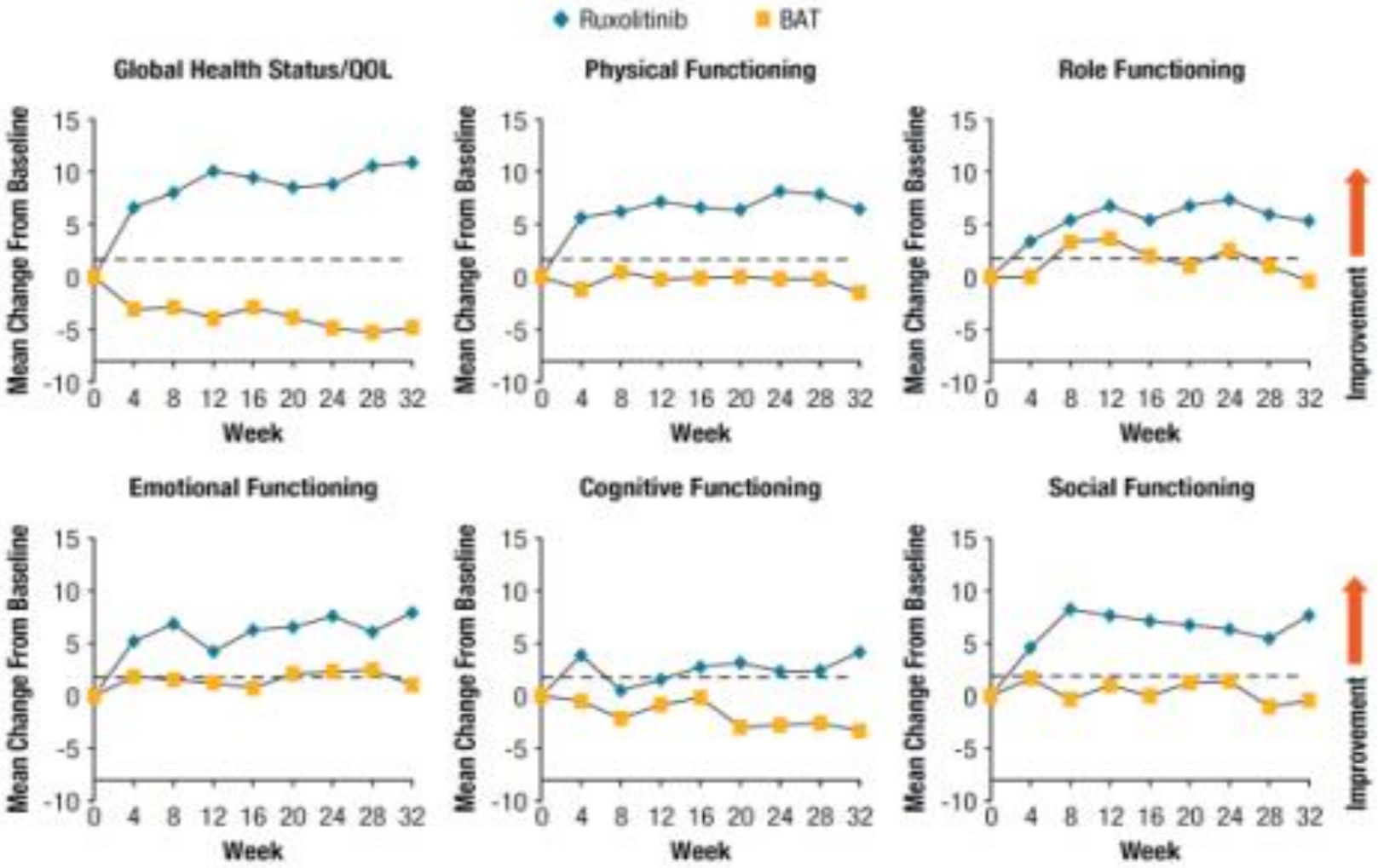
Primary endpoint, ≥50% improvement in total symptom score cytokine symptom cluster (TSS-C; sum of tiredness, itching, muscle aches, night sweats, and sweats while awake) at Week 16

Achieved by 43·4% rux vs. 29·6% HC ((odds ratio, 1·82; 95% confidence interval, 0·82-4·04; P = 0·139)

Ruxolitinib trend to improved symptoms versus HC BUT unexpectedly symptom improvement with HC

Mesa et al Br J Haematol. 2017 Jan;176(1):76-85

Ruxolitinib improves quality of life



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

5-year RESPONSE trial: adverse events

	208-Week (4-Year) Analysis			
	Ruxolitinib n = 110 Exposure, Patient-Years = 409		Crossover n = 98 Exposure, Patient-Years = 310	
Rate per 100 Patient-Years of Exposure	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Hematologic adverse events				
Anemia	9.3	1.0	9.4	0.6
Thrombocytopenia	4.6	1.0	1.3	0.3
Non-hematologic adverse events				
All infections	19.6	3.7	19.7	6.5
Herpes zoster infection	4.9	0.5	4.2	0.6
Pruritus	7.3	0.5	5.8	0
Diarrhea	7.1	0.2	3.2	0
Headache	6.1	0.5	5.5	0
Fatigue	5.1	0.2	4.2	0
Increased weight	5.6	0.7	4.2	0.3
Arthralgia	5.9	0.2	3.2	0.3
Muscle spasms	5.4	0.2	3.2	0
Dizziness	4.2	0.0	6.1	0

Kiladjian et al, ASH 2018

5-years RESPONSE trial: other adverse events of interest

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

Kiladjian et al, ASH 2018

5-years RESPONSE trial: thromboembolic adverse events

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

Kiladjian et al, ASH 2018

RESPONSE trials: limitations

Overall

−Complex study very hard to enroll patients
−Recruited patients with advanced disease
−Spleen volume reduction not of proven benefit in PV

Comparator group

−Some patients were treated with drugs they had already failed to respond to

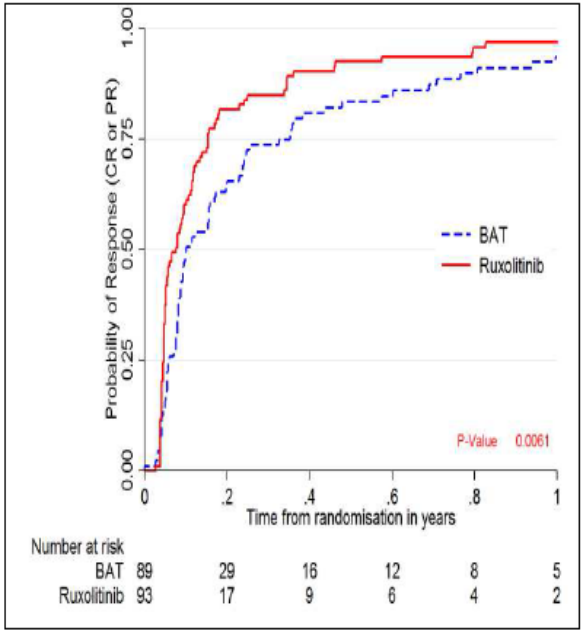
AND

−Cross-over design means long term effects upon thrombosis and transformation very difficult to assess

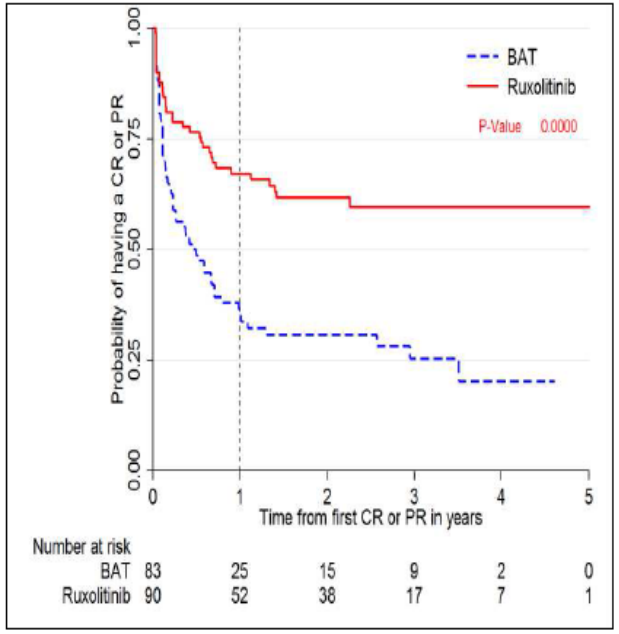
MAJIC Study

- **MAJIC PV is a UK randomised phase II study**
- **190 PV patients resistant/intolerant to HU.**
- **The primary objective is to evaluate the activity (CHR at 1 year) of RUX compared to BAT (mainly HU and IFN)**
- **The secondary objective is to evaluate the molecular response by *JAK2*V617F allele burden quantification**

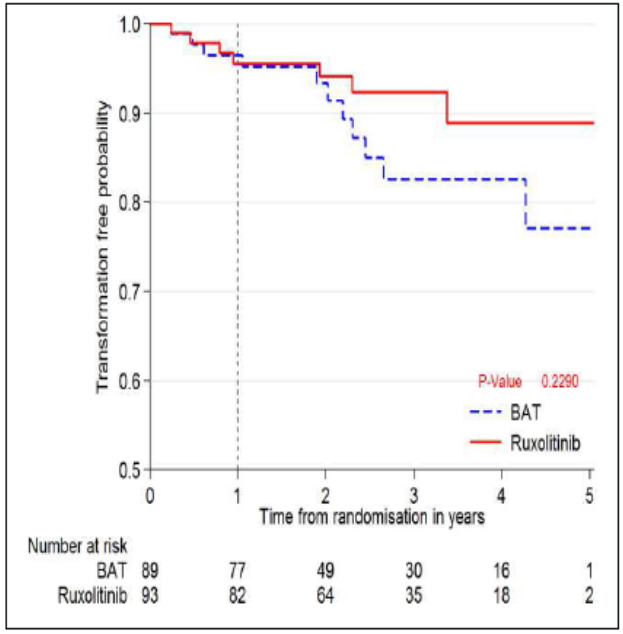
Speed of attaining response



Duration of overall response

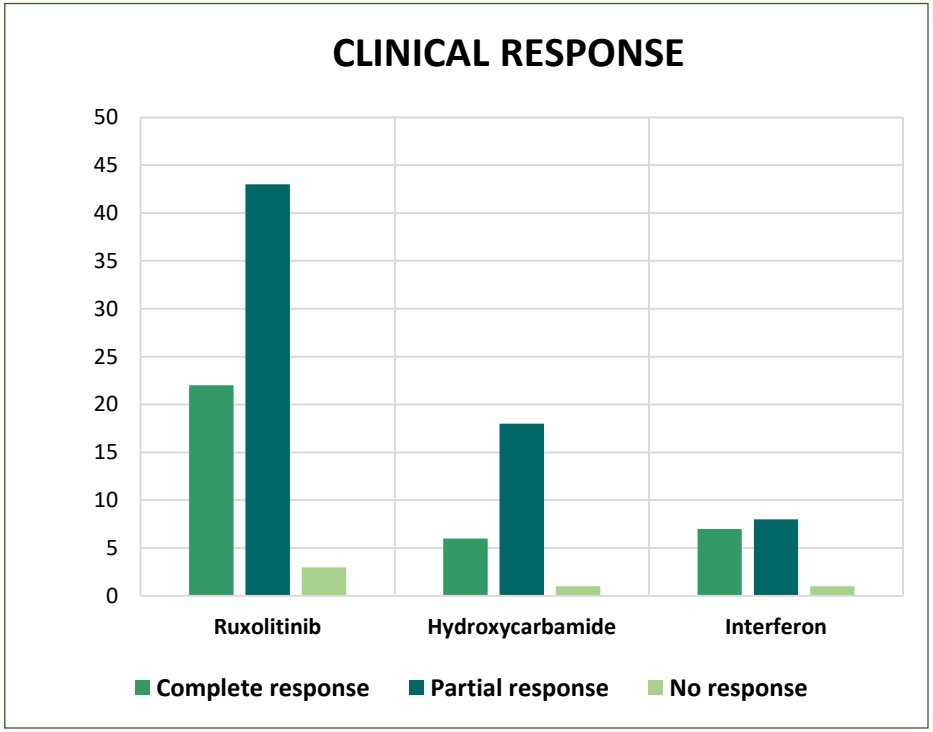


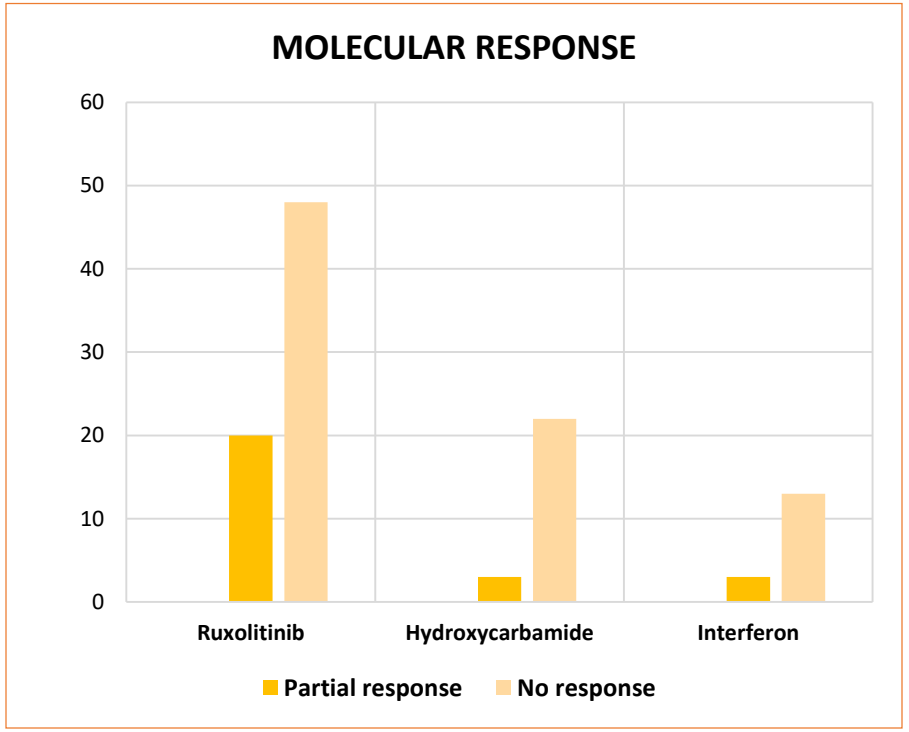
Transformation free survival



Curto-Garcia N. Jun 16, 2019; 267361; S1607

MAJIC-PV: Ruxo vs HU vs IFN
Haematological & Molecular Responses

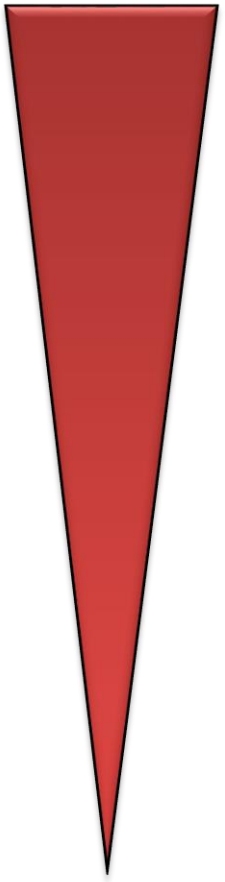




Curto-Garcia N. Jun 16, 2019; 267361; S1607

Ruxolitinib in PV – overview (1)

Strenght of evidence



- **Steady control of Hct at target level**
- **Control of leukocytosis**
- **Anti-inflammatory effect**
- **Reduction of *JAK2*V617F VAF**
- **Reduction of thrombotic events (impact on JAK2-mutated endothelium)**

Ruxolitinib in PV – overview (2)

- Rates (per 100 pt-yr) of thromboembolic events
  - 1.2 in RUX
  - 2.7 in crossover
  - 8.2 in BAT
- Exposure-adjusted rates of second malignancies
  - 7.0 in RUX; NMSC (5.1)
  - 4.5 in crossover; NMSC (2.7)
  - 4.1 in BAT; NMSC (2.7)
- Rates (per 100 pt-yr) of transformation to MF and AML
  - 2.1 and 0.2 in the RUX
  - 1.8 and 0.6 in crossover
  - 1.4 and 0.0 in BAT

Ruxolitinib – prescrivibilità AIFA

4.1 Indicazioni terapeutiche

Mielofibrosi (MF)

Jakavi è indicato per il trattamento della splenomegalia o dei sintomi correlati alla malattia in pazienti adulti con mielofibrosi primaria (nota anche come mielofibrosi idiopatica cronica), mielofibrosi post policitemia vera o mielofibrosi post trombocitemia essenziale.

Policitemia vera (PV)

Jakavi è indicato per il trattamento di pazienti adulti con policitemia vera che sono resistenti o intolleranti a idrossiurea.

4.2 Posologia e modo di somministrazione

Il trattamento con Jakavi deve essere iniziato solo da un medico esperto nella somministrazione di medicinali antitumorali.

Prima di iniziare la terapia con Jakavi si deve effettuare una conta ematica completa, inclusa una conta differenziale dei globuli bianchi.

Monitorare ogni 2-4 settimane la conta ematica completa, inclusa la conta differenziale dei globuli bianchi, fino alla stabilizzazione delle dosi di Jakavi, e in seguito come clinicamente indicato (vedere paragrafo 4.4).

Posologia

Dose iniziale
La dose iniziale raccomandata di ruxolitinib nella MF è di 15 mg due volte al giorno per i pazienti con una conta piastrinica tra 100.000/mm^3 e 200.000/mm^3 e di 20 mg due volte al giorno per i pazienti con una conta piastrinica >200.000/mm^3. La dose iniziale raccomandata di ruxolitinib nella PV è di 10 mg per via orale due volte al giorno.

Dosage and administration of Ruxolitinib in PV

- **Recommended starting dose: 10 mg BID**
- **Maximum dose: 25 mg BID**
- **Before therapy: screening as in MF patients**
  - **CBC**
  - **HBV, HCV, HIV serology**
  - **Investigate latent TBC**
  - **Educate the patient to report symproms that may be related to zoster reactivations**
  - **Evaluate renal/liver function**
  - **Spleen size by palpation & echography**
  - **Symptoms by MPN10-TSS**

THANKS FOR YOUR ATTENTION AND PLEASE ASK BUT NOT TOO MUCH

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