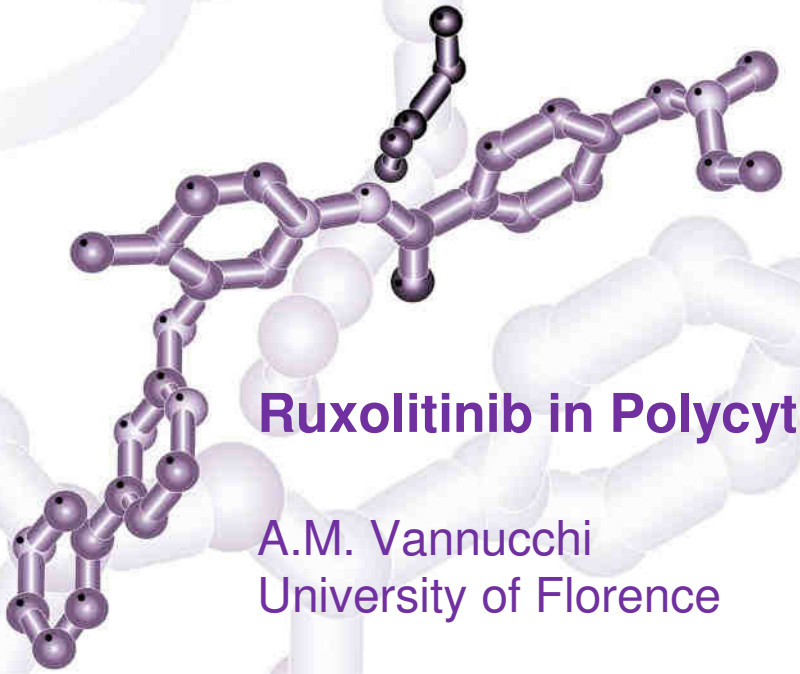


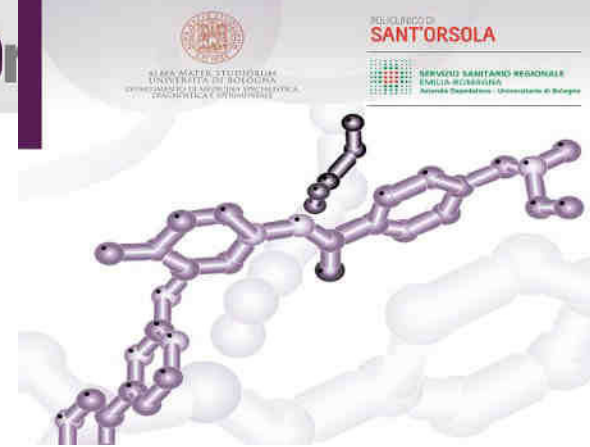
Ruxolitinib in Polycythemia Vera

A.M. Vannucchi
University of Florence

New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
May 18-20, 2022



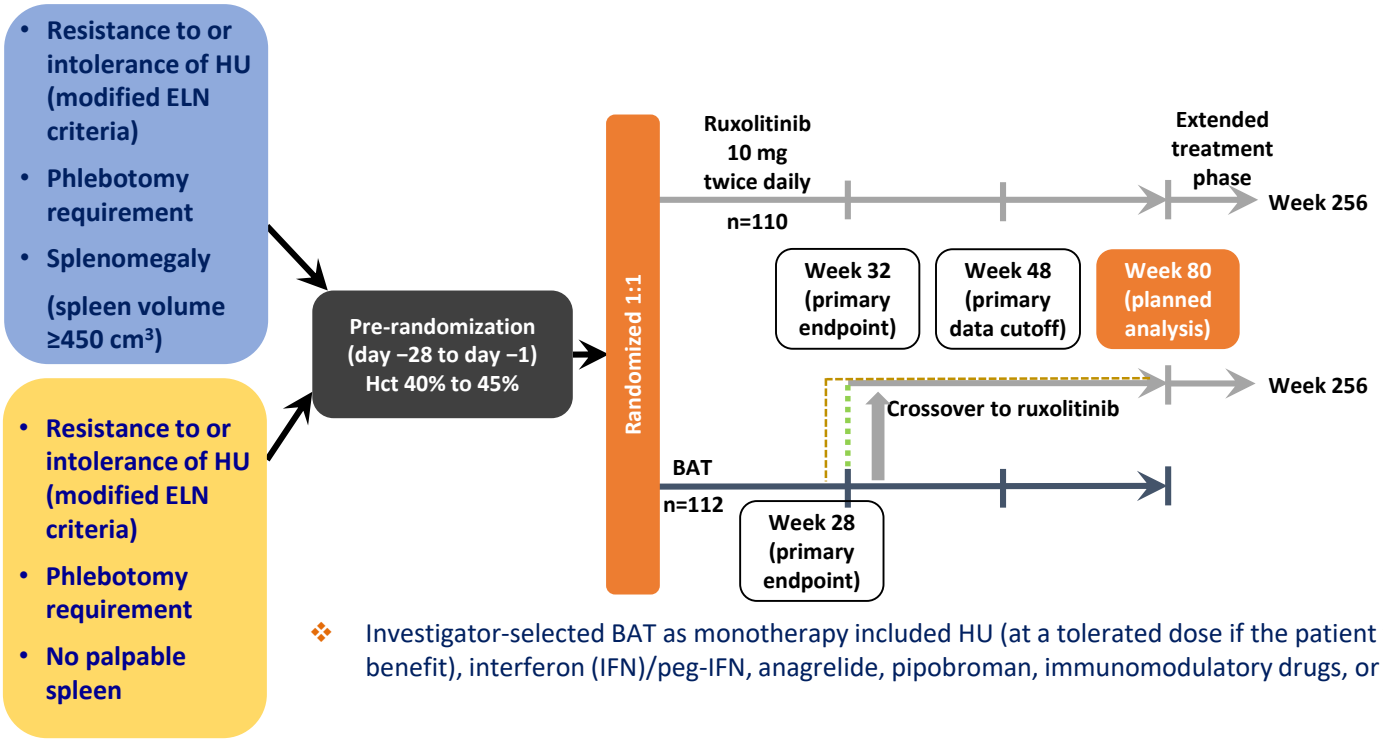
New Drugs in Hematology

Bologna,
Royal Hotel Carlton
January 17-19, 2022

Disclosures of NAME SURNAME

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis, BMS, Incyte, AbbVie, Blueprint, GSK					x	x	

RESPONSE & RESPONSE-2: Ruxolitinib in PV patients with Resistance/Refractoriness to Hydroxyurea



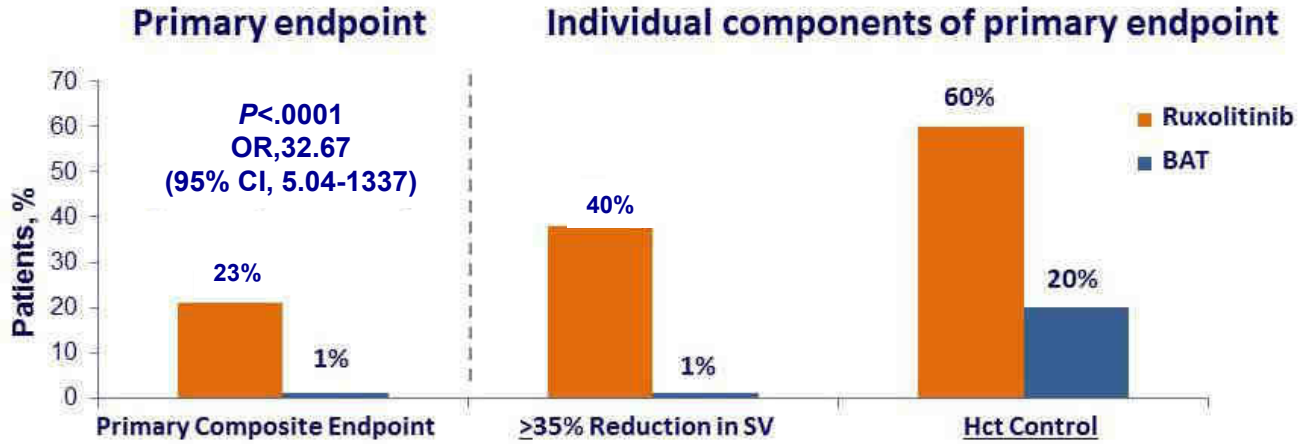
❖ Investigator-selected BAT as monotherapy included HU (at a tolerated dose if the patient were likely to receive benefit), interferon (IFN)/peg-IFN, anagrelide, pipobroman, immunomodulatory drugs, or observatio

- 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

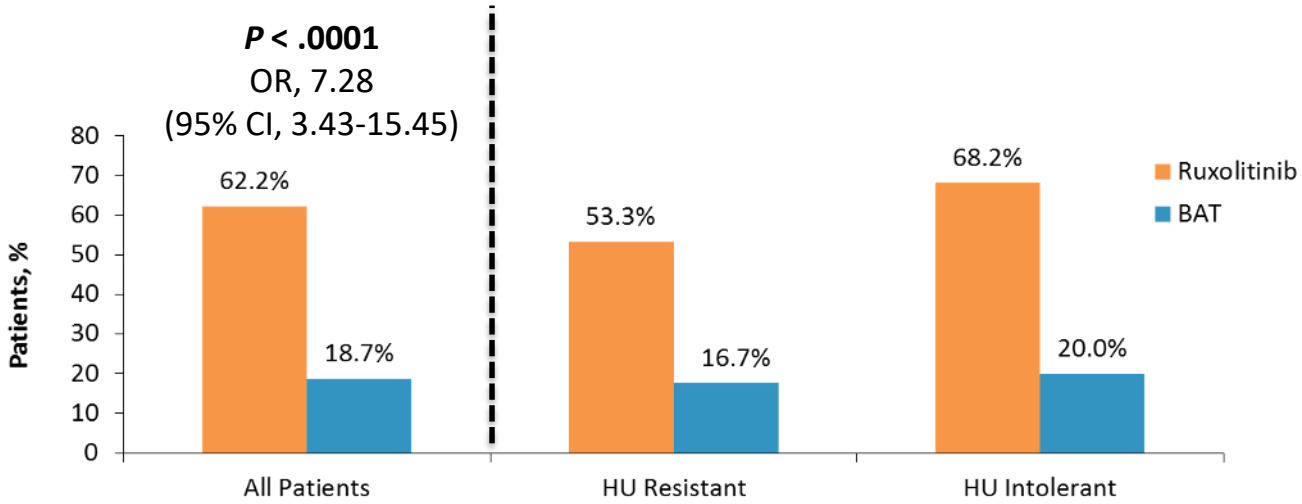
- **Primary endpoint (composite):** Percentage of patients who achieved both Hct control (Hct <45% and no phlebotomy) and spleen response (reduction of SV to ≤35% from baseline assessed by MRI) at week 32.



- 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

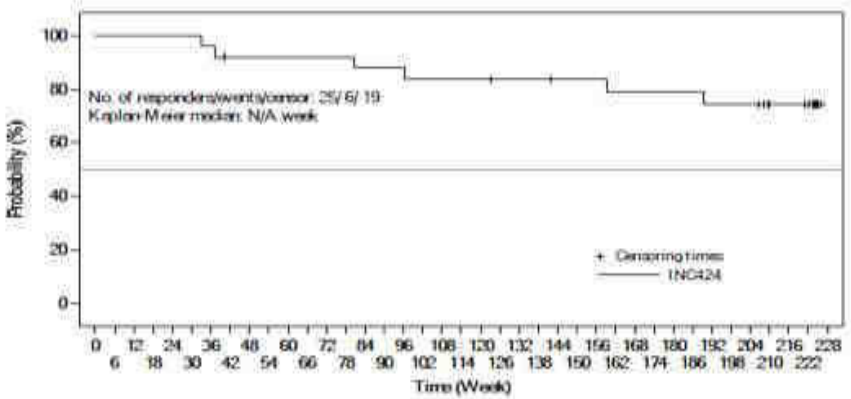


- RUX induces HCT control without phlebotomy in 62% of patients

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

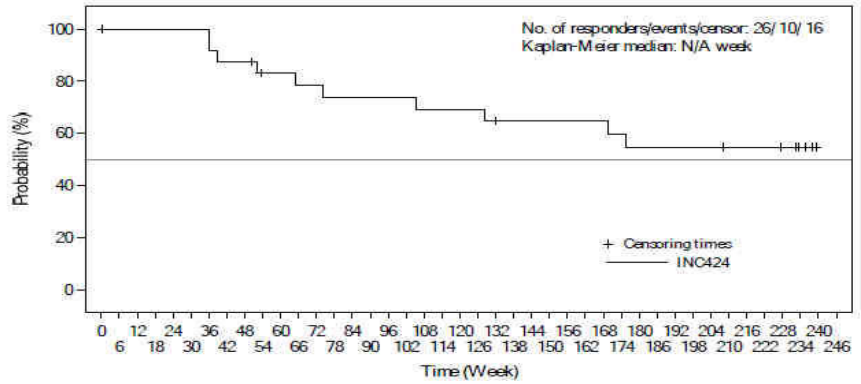
Long-term (5 years) Data from RESPONSE Study

Durability of Primary Response



- The KM estimate of duration of maintaining **PR** for 224weeks (from w32) was **0.74** (95%CI, 0.51-0.88); for **Hct** control **0.73**, for **spleen** volume **0.72**.

Durability of Complete Hematologic Response



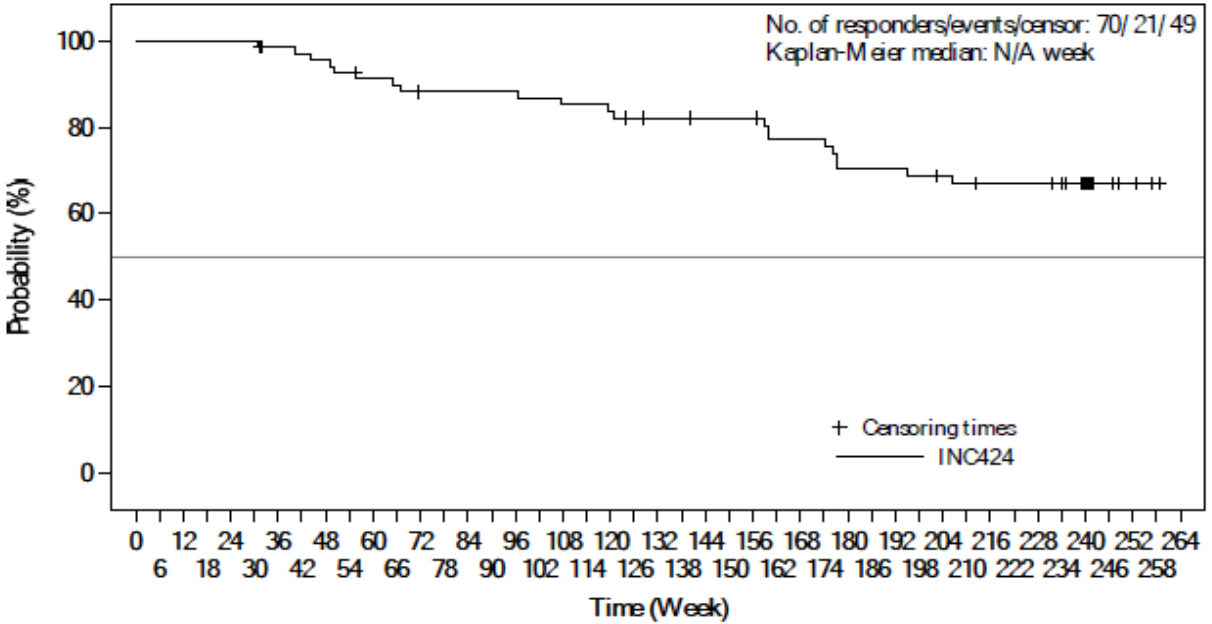
- The K-M estimate of duration of **CHR** for 224weeks (from w32) was **0.55** (95% CI: 0.32, 0.73).

Of the 87 patients with WBC >10 x10^9/L at baseline, 41% had a WBC <10 x10^9/L
Of the 54 patients with PLT >400 x10^9/L at baseline, 46% had PLT <400 x10^9/L

Kiladjian JJ et al. Lancet Haematol . 2020 Mar;7(3):e226-e237.

Long-term (5 years) Efficacy Data from RESPONSE Study

- Durability of Clinicohematologic Response



- The 5-yr probability of maintaining clinic-haematological response was 67% (95% CI: 54, 77) and the median duration was not reached

Kiladjian JJ et al. Lancet Haematol . 2020 Mar;7(3):e226-e237;

Long-term (5yr) Outcome with Ruxolitinib in RESPONSE

- Rates (per 100 pt-y) of thromboembolic events:
  - 1.2 in RUX
  - 2.7 in CrossOver
  - 8.2 in BAT
- Exposure-adjusted rates of second malignancies/NMSC:
  - 7.0/5.1 in RUX
  - 4.5/2.7 in CrossOver
  - 4.1/2.7 in BAT
- Rates (per 100 pt-y) 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

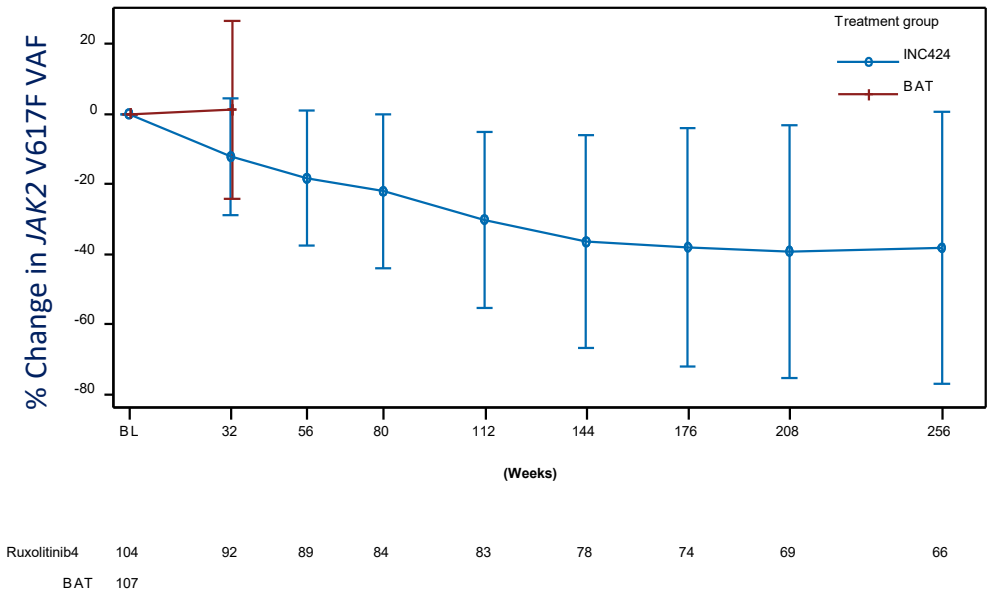
Kiladjian et al. Lancet Haematol. 2020 Mar;7(3):e226-e237.

Long-term (5 years) Safety Data from RESPONSE Study

INFECTIONS	Ruxolitinib Rate per 100 Patient-Year of Exposure N = 110 Exposure = 428.4 Patient-Year		BAT Rate per 100 Patient-Year of Exposure N = 111 Exposure = 73.6 Patient-Year		Crossover Rate per 100 Patient-Year of Exposure N = 98 Exposure = 329.9 Patient-Year	
Rate*	**All Grades**	**Grade 3 or 4**	**All Grades**	**Grade 3 or 4**	**All Grades**	**Grade 3 or 4**
All infections	**18.9**	**3.5**	**59.8**	**4.1**	**19.1**	**6.1**
Herpes zoster infection	4.7	0.5	0.0	0.0	3.9	0.6

Kiladjian JJ et al. Lancet Haematol . 2020 Mar;7(3):e226-e237.

Long-term (5 years) Molecular Data from RESPONSE Study



In the ruxolitinib arm, the mean percent change from baseline in VAF was **−38.12%** (SD: 38.64, n = 66) at week 256. It was −22.88% (SD: 40.5, n = 64) at week 224 in the crossover population.

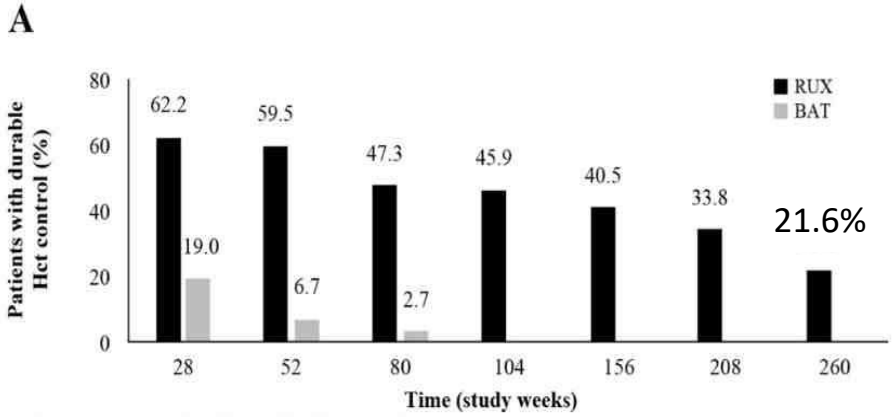
In the **MPN-SVT** Mynerva trial at a median of 5.5 yr of treatment reduction of *JAK2*V617F VAF>50% was documented in 40% of the pts, although it was not correlated with clinical parameters

Kiladjian JJ et al. Lancet Haematol . 2020 Mar;7(3):e226-e237; Paoli C et al. Abstrcat 1662P, Orlando ASH2019

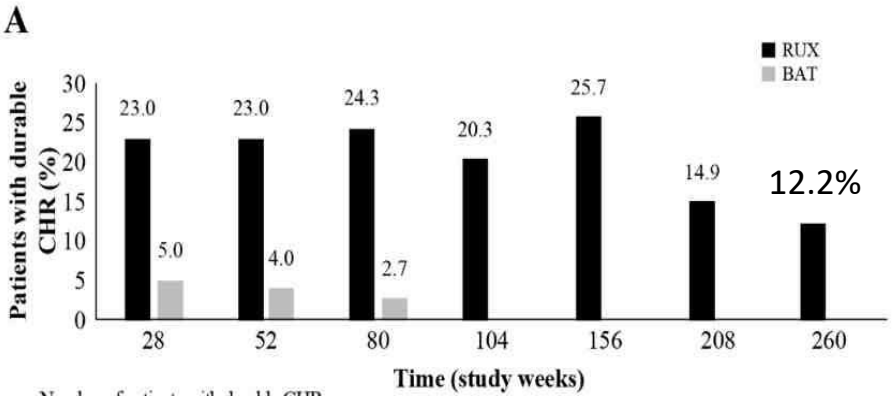
Long-term (5 years) Data from RESPONSE-2 Study

- Overall, 59 ruxolitinib-randomised, and 38 crossover patients completed 260 weeks of ruxolitinib treatment. No patient continued BAT after week 80.

- **Durable Hct control**



- **Durable CHR control**

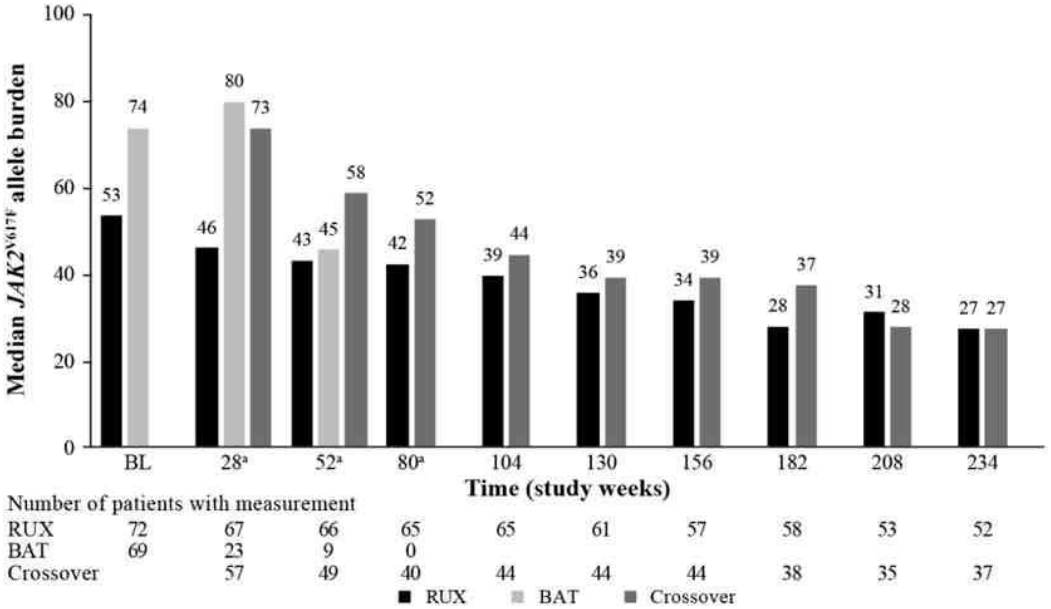


- **Time of loss to durable Hct control= nr**
- Phlebotomy rate was 2.5-5.5 fold lower with ruxo than BAT

- **Time of loss to durable CHR control= 34 w**

Passamonti F et al, Lancet Haematol 2022

Long-term (5 years) Molecular Data from RESPONSE-2 Study



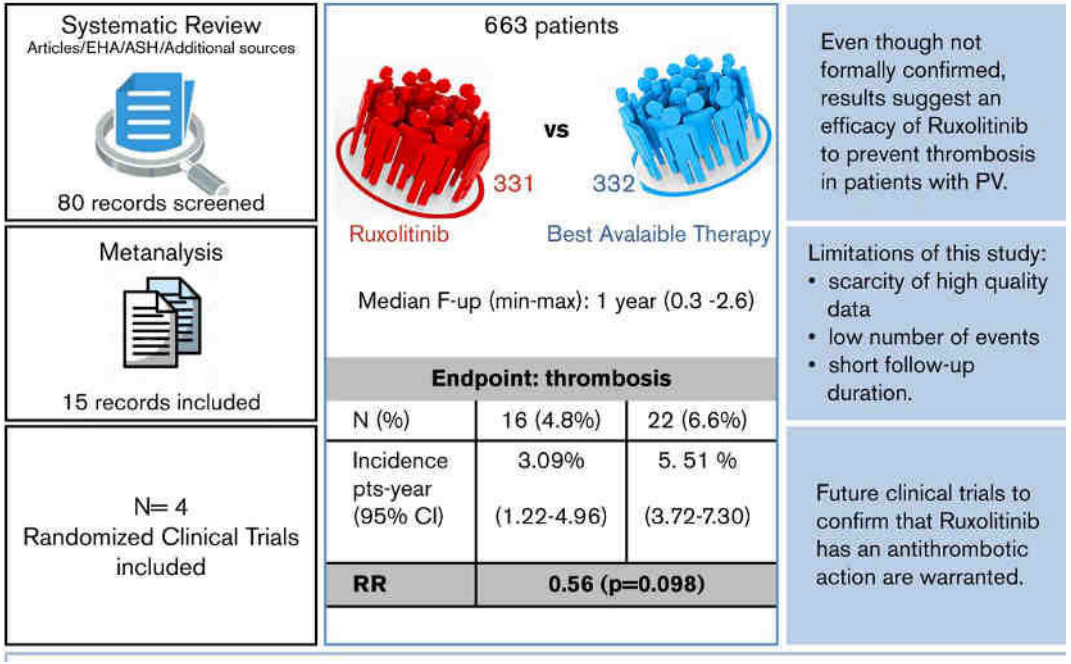
- **Overall survival rates** at ≥260 weeks were 95.75% (95% confidence interval 87.41–98.61) with ruxolitinib, and 90.67% (80.25–95.73) with BAT (crossover patients not censored); median overall survival was not reached in either arm.

Long-term (5yr) Outcome with Ruxolitinib in RESPONSE-2

- Rates (per 100 pt-y) of thromboembolic events:
  - 1.5 in RUX
  - 2.9 in CrossOver
  - 3.7 in BAT
- Exposure-adjusted rates of cancers/NMSC:
  - 4.4/9.0 in RUX
  - 4.5/6.0 in CrossOver
  - 7.7/1.0 in BAT
- Rates (per 100 pt-y) of infectious events:
  - 14.7 in the RUX
  - 15.1 in CrossOver
  - 33.7 and 0.0 in BAT

Kiladjian et al. Lancet Haematol. 2020 Mar;7(3):e226-e237.

Ruxolitinib for the prevention of thrombosis in PV: a systematic review and meta-analysis

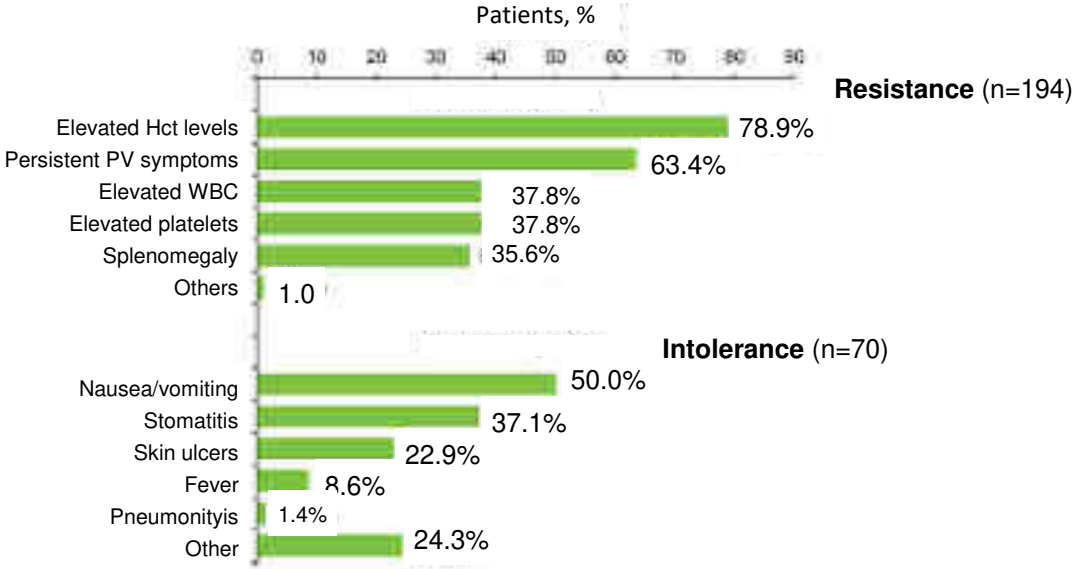


- The number of thrombotic events reported with ruxolitinib was consistently lower than that with BAT in our sample, but, globally, the difference did not reach significance (*P* = .098).
- Hard evidence in favor of ruxolitinib is lacking; a clinical trial on selected patients at high risk of thrombosis would be warranted, but its feasibility is questionable.

Masciulli A et al, Blood Adv 2021

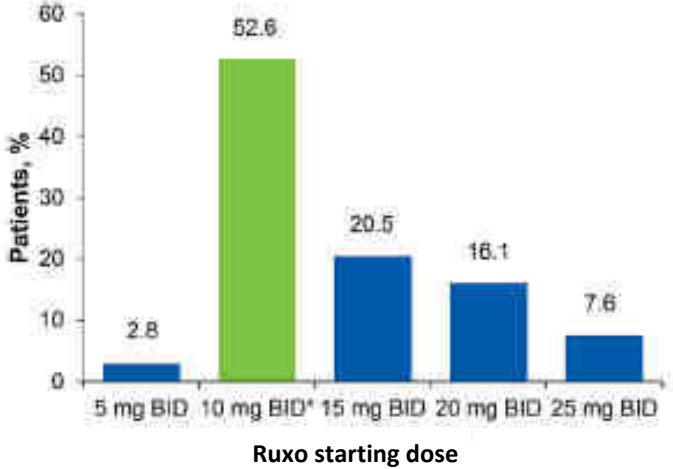
Real-Word Usage of Ruxolitinib in PV in the US

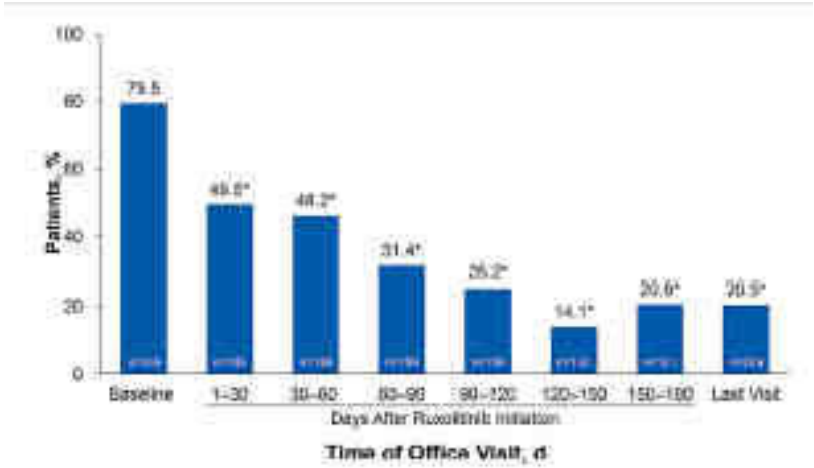
- A medical chart review of 249 patients to investigate **reasons for switching treatment to ruxolitinib** and ruxolitinib treatment patterns



Altomare I et al, Clin Lymph Myel Leuk, 2021

Real-Word Usage of Ruxolitinib in PV in the US





- Median duration of ruxo therapy: 31.4 mo (14.5-40.4)
- Discontinuation of ruxo: 38.6%
- Median time to ruxo discontinuation: 10.9 mo (6.3-17.4)

- Pts with Hc control at last visit: 61.4%

Altomare I et al, Clin Lymph Myel Leuk, 2021

Real-Word Analysis of Outcomes in Ruxolitinib Treated Patients

- A retrospective, real-world analysis of 377 patients with resistance/intolerance to HU from the Spanish Registry of PV according to subsequent treatment with ruxolitinib (n = 105) or best available therapy (BAT; n = 272).
  - No difference in OS, hazard ratio 0.8 (95% CI, 0.4-1.7; P = .6).
  - No difference in MFS, hazard ratio 0.8 (95% CI, 0.4-2.3; P = .9).

	Ruxolitinib (251 Person-y)		BAT (1272 Person-y)		
	No. of Events	Incidence Rate[a]	No. of Events	Incidence Rate[a]	*P*
Arterial thrombosis[b]	1	0.4	29	2.3	.03
Venous thrombosis[c]	2	0.8	14	1.1	.7
Major bleeding[d]	2	0.8	11	0.9	.9

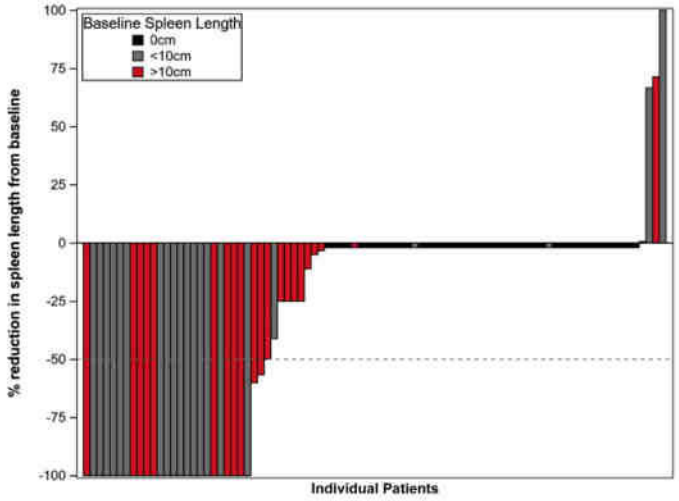
- No difference in incidence of second cancers (IR 2.4 vs 2.7) including cutaneous carcinoma (IR 1.2 vs 1.3)

Alvarez-Larran A et al,Cancer 2022

Real-World Outcomes of Ruxolitinib Treatment for Polycythemia Vera*

*, multi-center retrospective analysis of 126 PV patients receiving ruxolitinib at 11 participating sites across the US

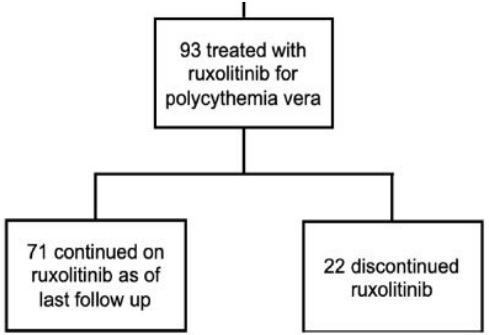
- Median FU: 22.4 months (range, 0-63.0 months).
- At 32 w of ruxolitinib, the % of patients who received ≥1 phlebotomy was significantly decreased compared with before ruxolitinib (37% vs. 56%; RR, 0.66; 95% CI, 0.52-0.84; P < .001).
- A total of 9.5% of patients discontinued ruxolitinib owing to treatment-emergent adverse events, and 81.7% of patients were receiving ruxolitinib at last known follow-up.



- Palpable spleen decreased at 32-w from 48% to 20% of the pts [RR, 2.45; 95% CI, 1.70–3.53; P < .0001]

Coltoff A et al. Clin Lymph Myerl Luek 2020;20:697-703

Ruxolitinib Discontinuation in PV: Real World Study



- The median time to ruxo discontinuation was not reached. At 6 and 12 mo, 89 % (95 % CI 83–96 %) and 86 % (95 % CI 79–94 %) of patients, respectively, were still on ruxolitinib.
- Patients who discontinued ruxolitinib were older at time of treatment initiation (67.5 versus 64.8 years, p = 0.0058), but had otherwise similar patient and disease characteristics

Reasons for discontinuation.

Reason	N (%)
Myelosuppression	3 (14 %)
Dizziness	3 (14 %)
Confusion/difficulty concentrating	3 (14 %)
Headache	2 (9 %)
Nausea/Vomiting/Diarrhea	2 (9 %)
Lymphoma	2 (9 %)
Transformation to myelofibrosis	1 (5 %)
Weight gain	1 (5 %)
Bruising	1 (5 %)
Nail/hair changes	1 (5 %)
Patient decision	1 (5 %)
Unknown	9 (41 %)

Multiple reasons were listed for 5 patients (23 %).

- NO thrombotic event nor progression after Ruxo discontinuation with 1 pts who died.

Tremblay D et al, Leuk Res 2021

ELN 2022 Recommendations for the Management of PV

- **For second line in patients receiving hydroxyurea:**

  Either ruxolitinib or interferon-α should be chosen on the basis of individual clinical features – in particular, age, spleen size, symptoms, history of skin cancers, and patient' preferences)

Marchetti M, Lancet Haematol 2022; 9:e301