Azienda Ospedaliero Universitaria Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE

Nona Giornata Fiorentina dedicata ai pazienti con malattie mieloproliferative croniche

Sabato 20 maggio 2023

"Policitemia vera: 2 linea"

Francesco Passamonti

Università di Milano
I.R.C.C.S. Policlinico di Milano

Quando bisogna pensare ad una seconda linea: (ELN 2022): raccomandato

- Intolleranza all'HU per grado 3-4 o tossicità prolungata grado 2 (sintomi mucocutanei, gastrointestinali, febbre o polmonite) a qualsiasi dose di HU
- Intolleranza all'HU per anemia, piastrinopenia, leucopenia alla dose più bassa di HU per ottenere una risposta
- Sviluppo di tumori cutanei non melanoma
- Sviluppo di eventi vascolari: sanguinamento clinicamente rilevante, trombosi venosa o trombosi arteriosa

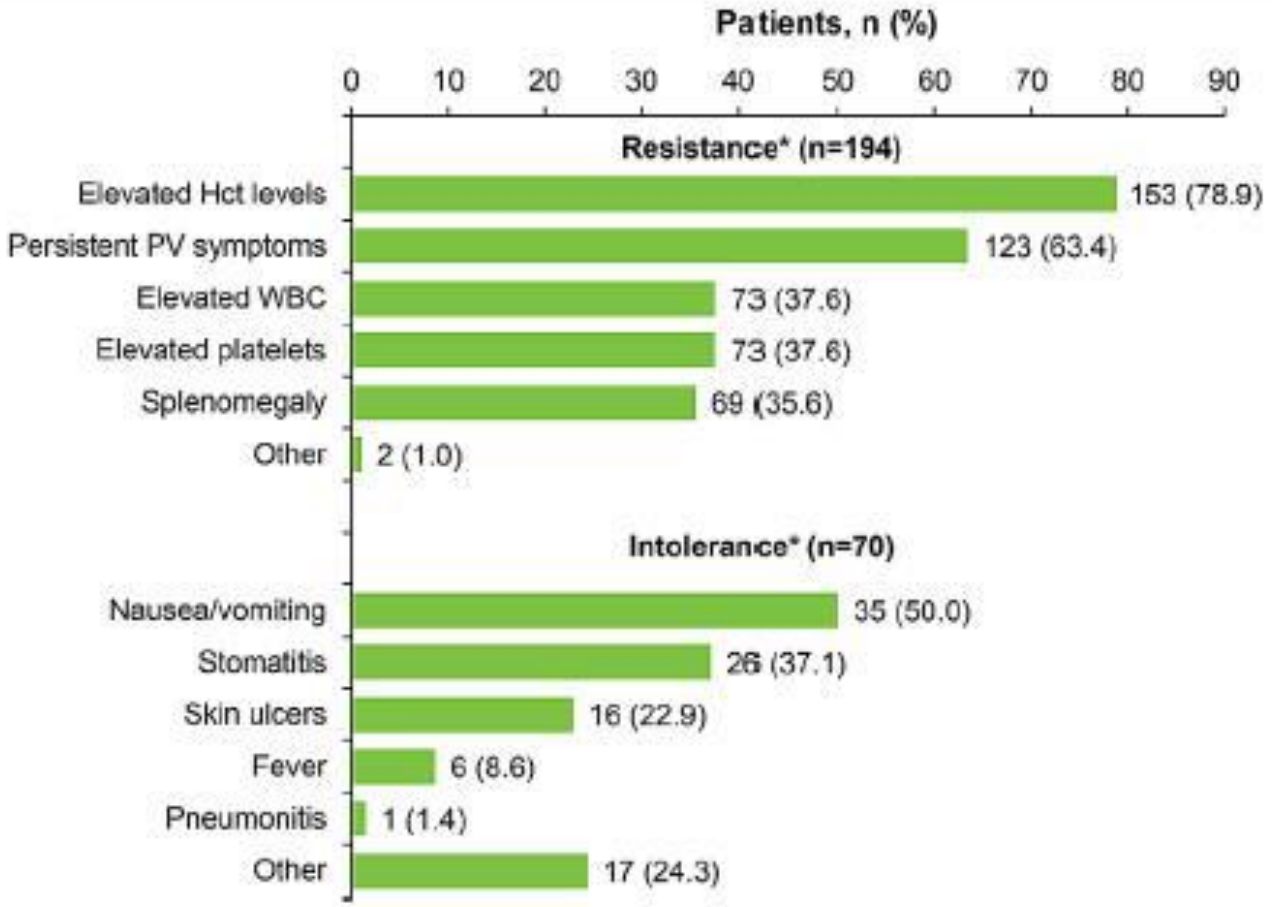
Marchetti et al. Lancet Haematology Vol 9 April 2022

Quando bisogna pensare ad una seconda linea: (ELN 2022): da considerare

- Trombocitosi persistente con PLT >1milione/mmc, sintomi microvascolari, o entrambi, persistente per > 3 mesi
- Splenomegalia sintomatica o progressiva: aumento delle dimensioni della milza > 5 cm in 1 anno
- Aumento progressivo e leucocitosi persistente
- Controllo HCT insufficiente: >=6 salassi/anno per mantenere HCT <45%
- Sintomi persistenti correlati al PV: TSS ≥ 20; Punteggio prurito ≥10 per almeno 6 mesi

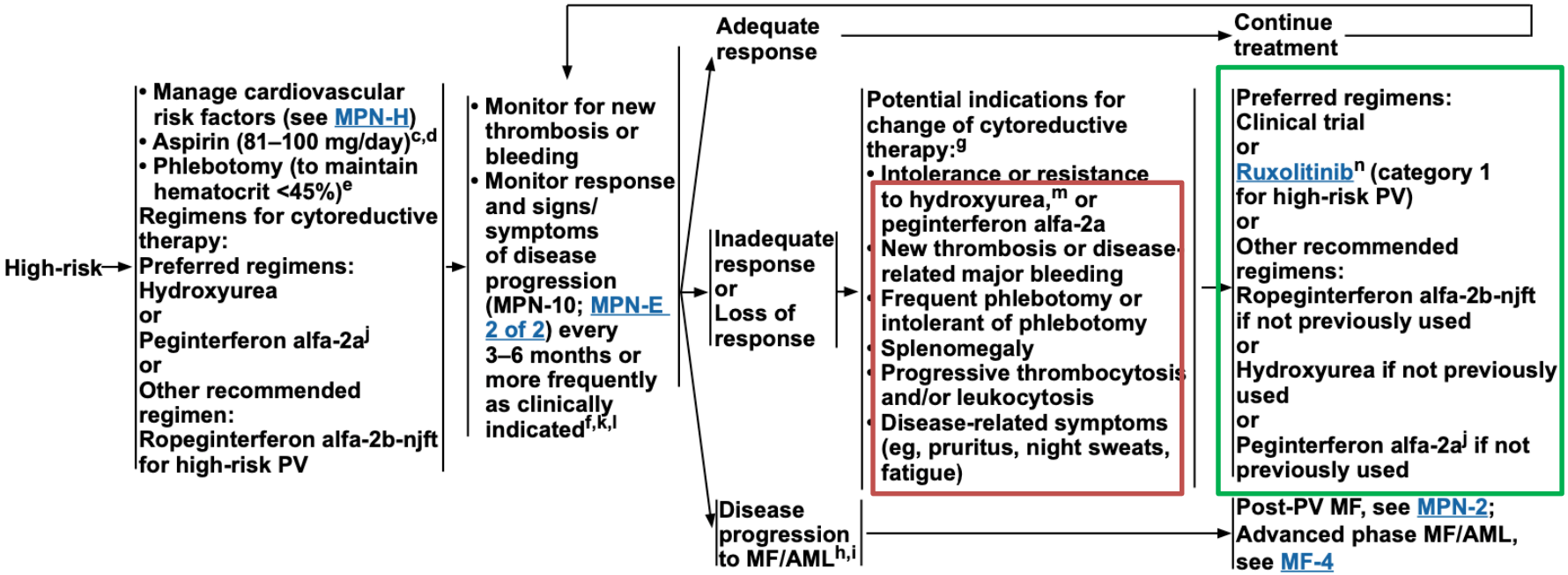
Marchetti et al. Lancet Haematology Vol 9 April 2022

Cause di cambio terapia da HU a RUX



Altomare I et al Clin Lymphoma Myeloma Leuk 2021

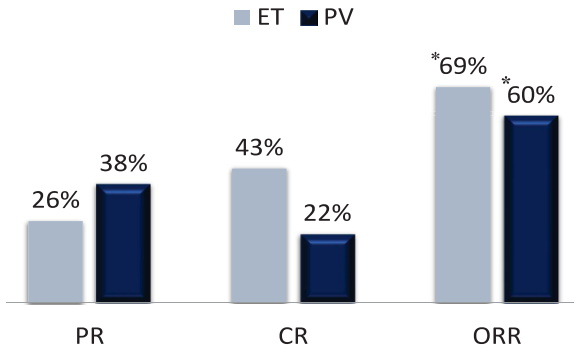
Le lineeguida per PV dell'NCCN



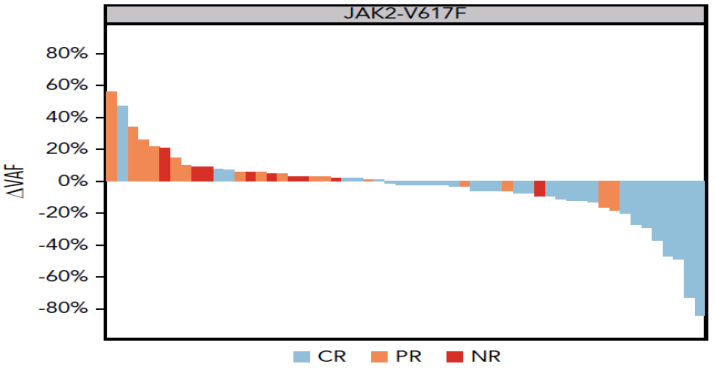
1-year results of Peg-interferon-α2a as second-line therapy in 50 HR PV: the MPD-RC 111 phase 2 study

CR means:

- PLT <400 x10^9/L, WBC <10 × 10^9/L
- HCT <45% without phlebotomy
- Resolution of splenomegaly and of disease-related symptoms

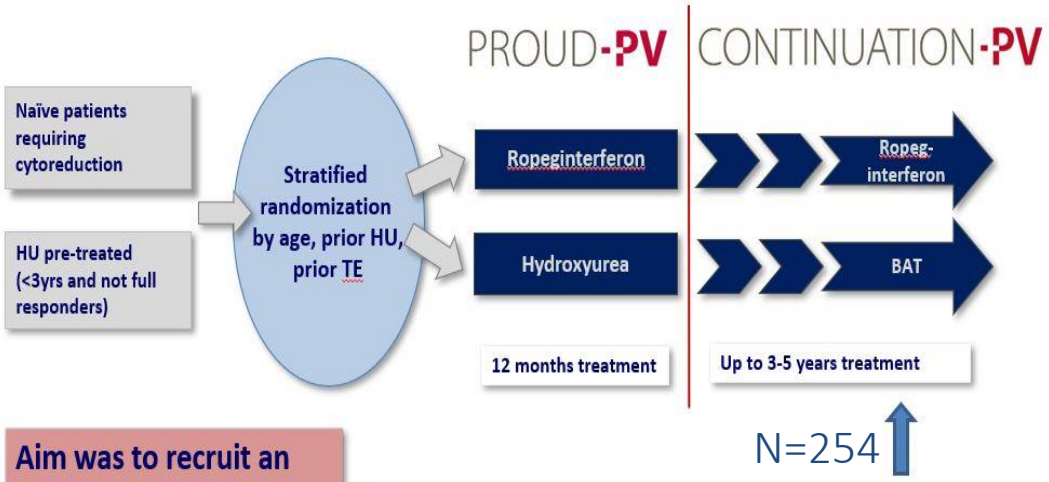


- HCT <45%: 46%
- Phlebotomy independency: 37%
- Splenomegaly normalization: 32%
- >20% VAF reduction 41.3%



Yacoub et al, Blood. 2019 Oct 31;134(18):1498-1509.

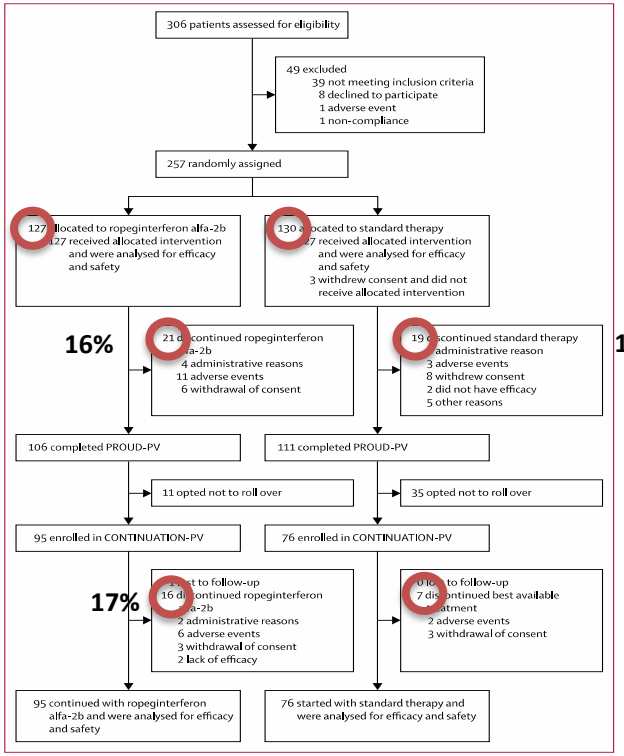
RopegIFN alfa-2b in HR-PV: the PROUD/CONTINUATION-PV phase 3 study



Aim was to recruit an "early PV" population.

Longitudinal interim analysis after 36 months of treatment (**PROUD-PV and CONTINUATION-PV**) in patients enrolled in CONTINUATION-PV Study:

- **Efficacy data up to 36 months**
- **All available safety data (mean 3.8 years)**



Gisslinger et al, Lancet Haematol . 2020 Mar;7(3):e196-e208.

PROUD/CONTINUATION-PV: baseline characteristics

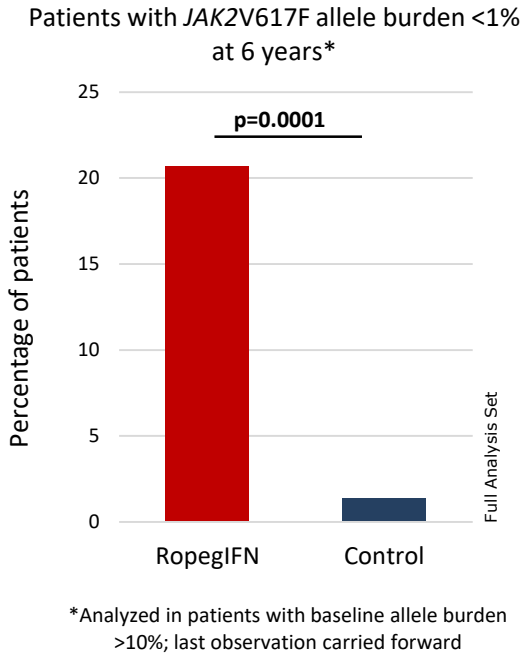
	PROUD-PV		CONTINUATION-PV*	
	Ropeginterferon alfa-2b (n=127)	Hydroxyurea (n=127)	Ropeginterferon alfa-2b (n=95)	Best available treatment (n=76)
Female	68 (54%)	67 (53%)	48 (51%)	40 (53%)
Male	59 (46%)	60 (47%)	47 (49%)	36 (47%)
Age, years				
Median	60·0 (52·0–66·0)	60·0 (48·0–67·0)	58·0 (50·0–64·0)	59·0 (49·0–65·5)
Range	30–85	21–81	30–85	32–79
Hydroxyurea pretreated	45 (35%)	37 (29%)	30 (32%)	20 (26%)
Median duration of previous hydroxyurea therapy, months†	10·2 (2·1–21·3)	7·9 (2·7–19·2)	9·5 (2·8–25·1)	8·2 (2·6–23·0)
Median duration of polycythaemia vera, months‡	1·9 (0·7–11·2)	3·6 (0·7–20·0)	1·8 (0·6–6·8)	1·6 (0·7–15·1)
Previous thromboembolic event	25 (20%)	23 (18%)	21 (22%)	14 (18%)
Positive status for *JAK2* Val617Phe mutation§				
Number	126 (99%)	125 (98%)	94 (99%)	74 (97%)
Mean allele burden, %	41·9% (24)	42·8% (24)	42·8% (23)	42·9% (23)
Median haematocrit, %	47·1% (44·2–51·3)	48·0% (45·0–52·2)	47·7% (44·4–52·0)	49·9% (46·2–53·1)
Median platelet count, 10^9/L	485·0 (350·0–671·0)	452·0 (329·0–666·0)	488·0 (350·0–701·0)	451·0 (329·0–678·5)
Median leucocyte count, 10^9/L	10·6 (8·0–13·4)	10·5 (7·9–14·5)	10·9 (8·0–14·6)	11·3 (8·7–15·1)
Median spleen size, cm	13·1 (11·0–15·0)	13·0 (11·5–15·2)	13·5 (11·5–15·0)	12·8 (11·3–15·5)
Presence of splenomegaly¶	12 (9%)	15 (12%)	7 (7%)	8 (11%)

Data are n (%), mean (SD), median (IQR). *Baseline in CONTINUATION-PV was defined as the end of treatment (month 12) in PROUD-PV. †Duration of previous hydroxyurea therapy was assessed from start of therapy until the time of screening in PROUD-PV. ‡Duration of polycythaemia vera was assessed from diagnosis until the time of screening in PROUD-PV. §Data were not available for one patient in the ropeginterferon alfa-2b group, and for two patients in the control group in PROUD-PV at baseline. Positive status for *JAK2* Val617Phe mutation was confirmed at subsequent visit. ¶Splenomegaly as assessed by investigator.

Gisslinger et al, Lancet Haematol . 2020 Mar;7(3):e196-e208.

PROUD/CONTINUATION-PV: potential disease modification at 6 years

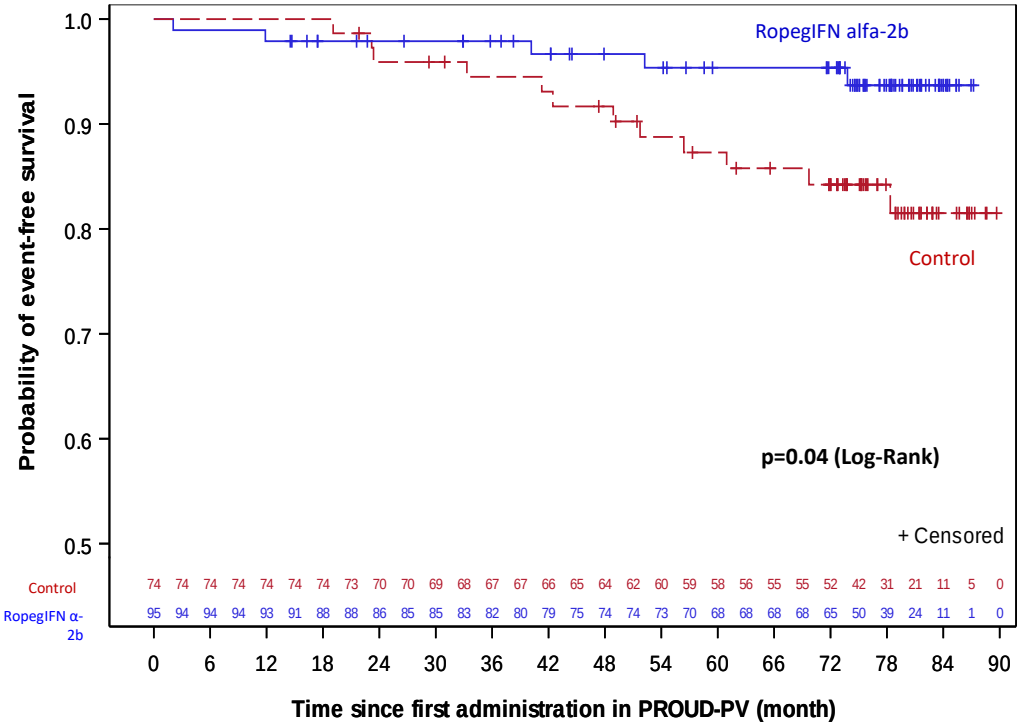
- After 6 years of treatment, the *JAK2* V617F allele burden decreased to <1% in 20.7% of patients in the ropeginterferon alfa-2b arm.
- In contrast, only 1.4% of patients in the control arm achieved an allele burden <1% at 6 years of treatment (p=0.0001).



Gisslinger et al. EHA 2022

PROUD/CONTINUATION-PV: Event-free survival

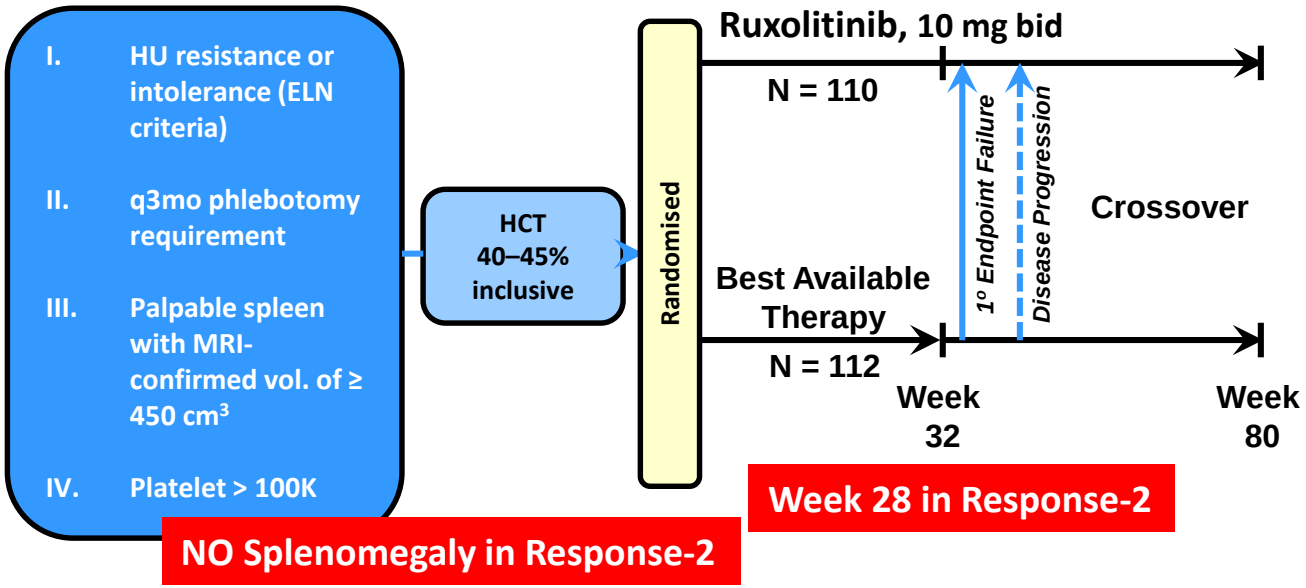
Risk events: death, disease progression and thromboembolic events



The probability of event-free survival was significantly higher among patients treated with ropeginterferon alfa-2b compared to the control arm (maximum treatment period 7.3 years)

Gisslinger et al. EHA 2022

Ruxolitinib as 2nd line in PV: the Response trials

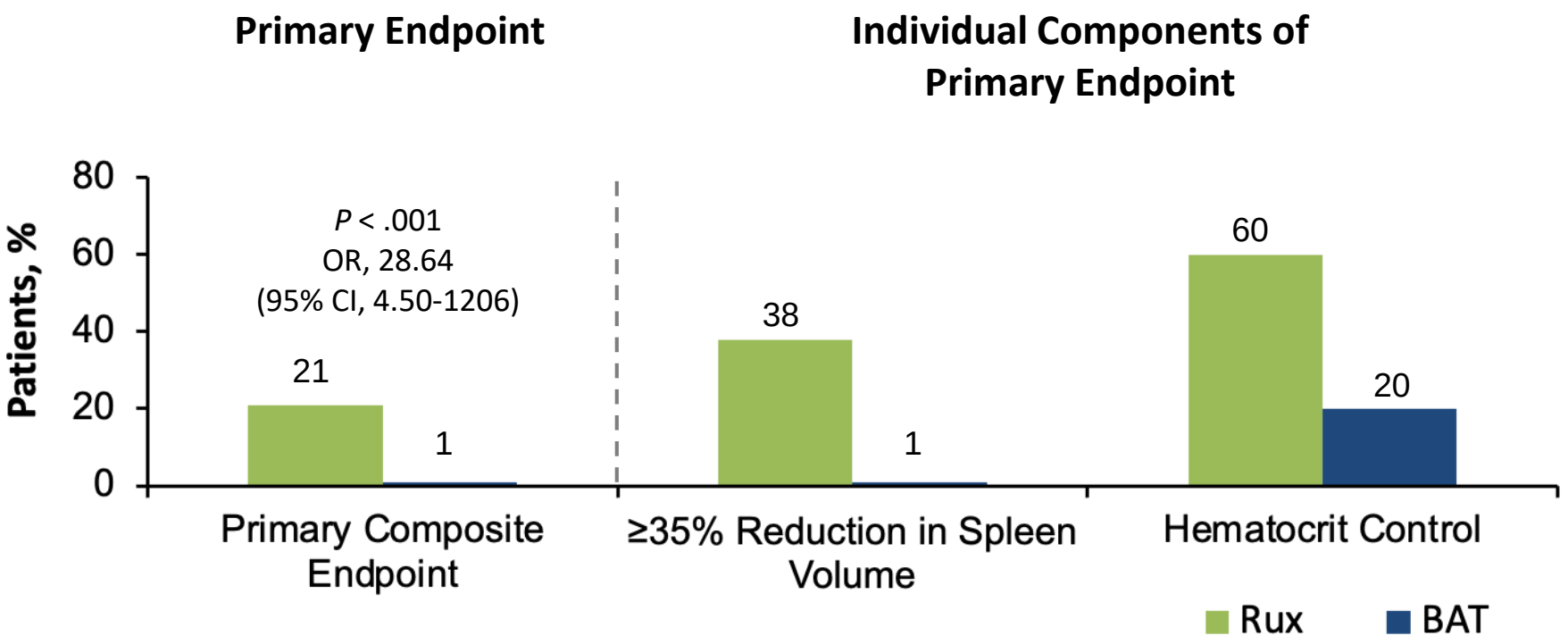


- Primary composite endpoint: haematocrit control (phlebotomy independence from week 8 to 32, with ≤ 1 phlebotomy post randomization) in the absence of phlebotomy and 35% reduction in spleen volume at week 32 (this latter absent in Response 2)

Vannucchi et al., NEJM. 2015; Passamonti et al., Lancet Oncol. 2017

RUX induce il controllo HCT senza flebotomia e SVR35 nel 21% dei pazienti PV che hanno fallito HU

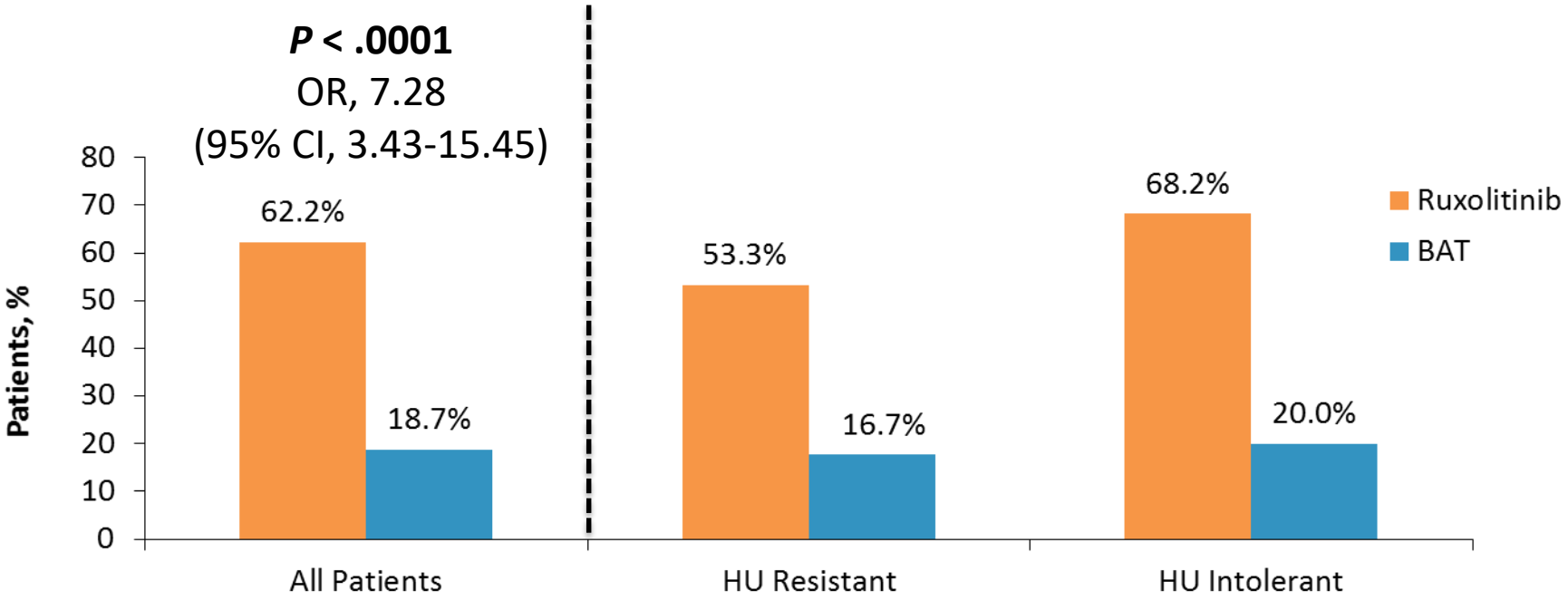
The RESPONSE trial



Vannucchi et al, N. Engl. J. Med. 2015

RUX induce il controllo dell'HCT senza flebotomia nel 62% dei pazienti PV che hanno fallito l'HU senza splenomegalia

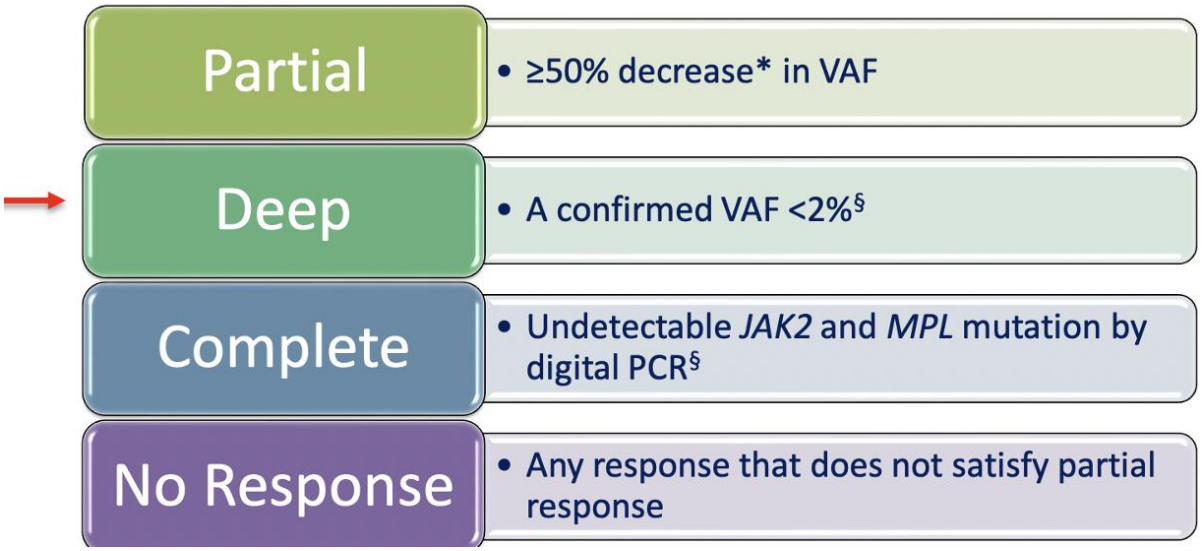
RESPONSE-2 trial



Passamonti et al, Lancet Oncol. 2017

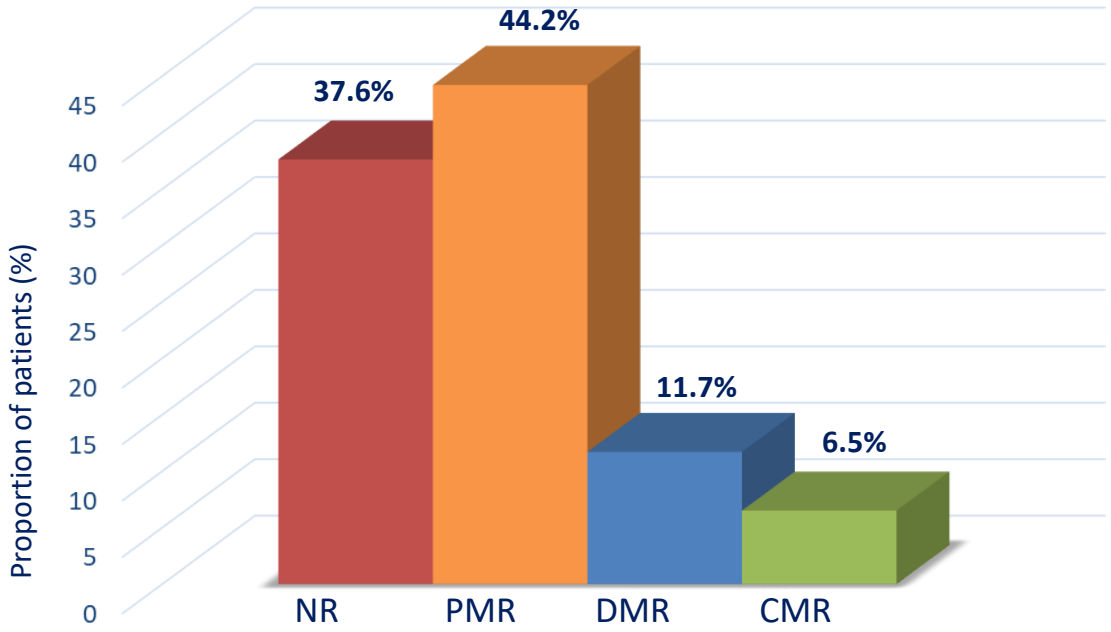
Risposta molecolare di JAK2 in pazienti con PV & ET trattati con RUX

- Sono stati inclusi 77 pazienti, 65 PV (84,4%) e 12 ET (12,6%) con una valutazione dell'intervallo circa-annuale di JAK2 V617F VAF mediante PCR digitale o RTQ-PCR ad alta sensibilità



Guglielmelli et al. ASH 2022

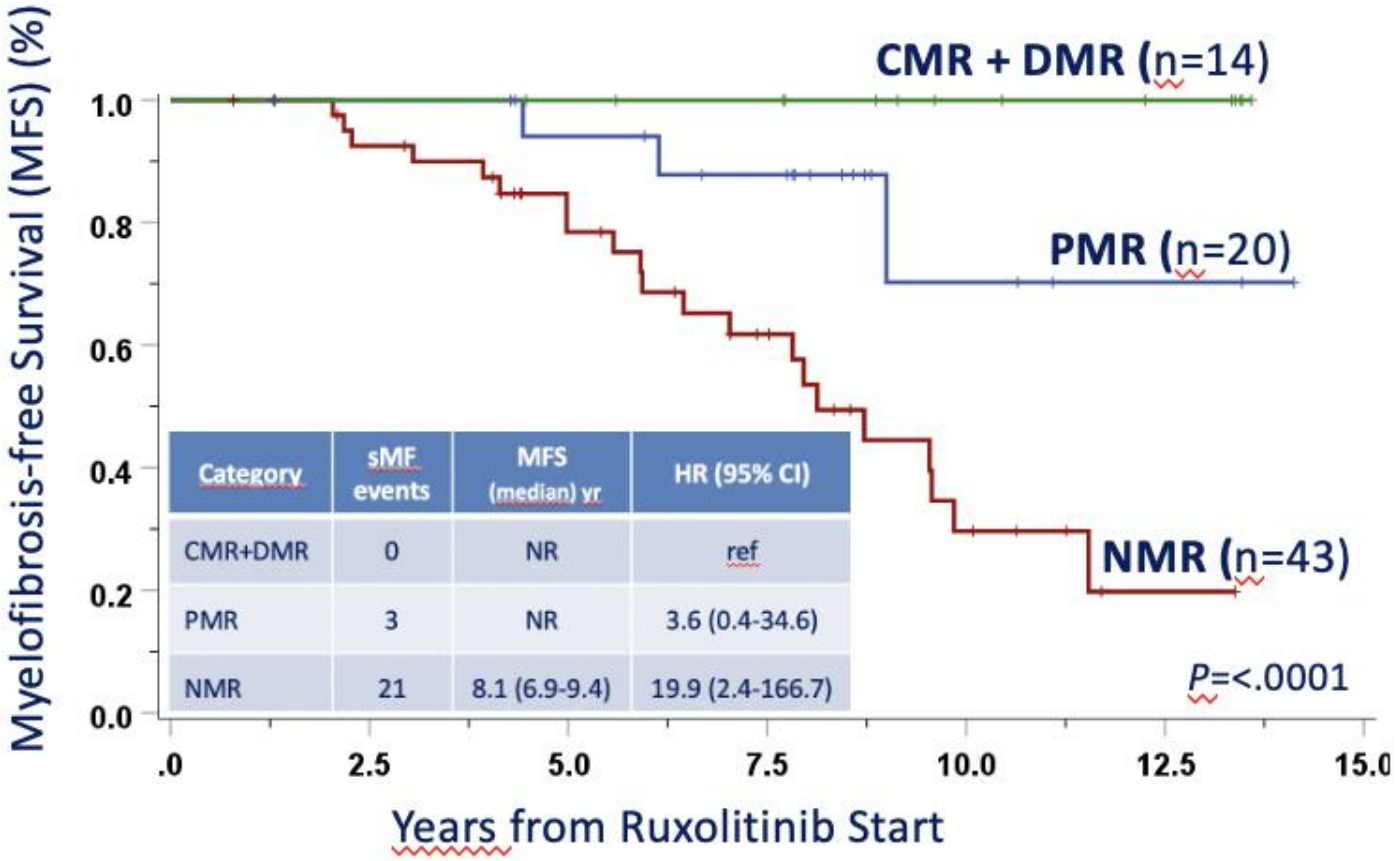
Risposta molecolare di JAK2 V617F in PV & ET



- Il tempo mediano a CMR e DMR è stato di 4,6 anni (1,1-7,6 anni) e 5,0 anni (2,1-12,1 anni.

Guglielmelli et al. ASH 2022

La risposta molecolare è associata a una sopravvivenza libera da MF più lunga



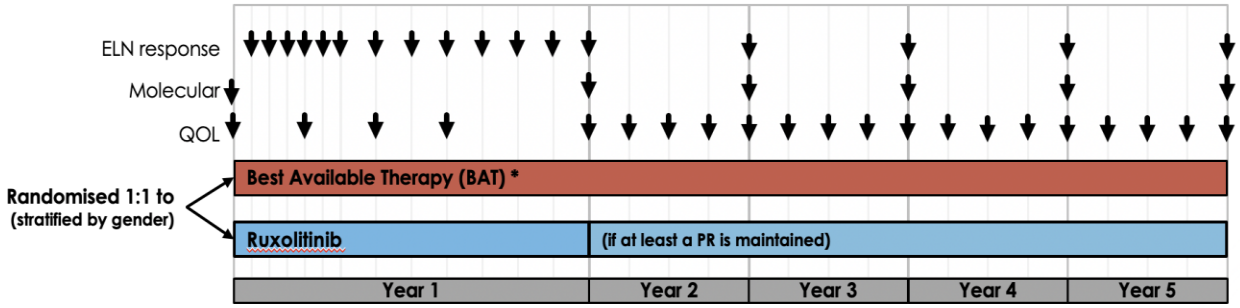
Category	sMF events	MFS (median) yr	HR (95% CI)
CMR+DMR	0	NR	ref
PMR	3	NR	3.6 (0.4-34.6)
NMR	21	8.1 (6.9-9.4)	19.9 (2.4-166.7)

- 24 patients (31.1%) progressed to sMF after a median of 6.0y (2-11.5). 34% were PV and 16.6% ET.

Guglielmelli et al. ASH 2022

MAJIC-PV randomised trial: RUX vs. BAT for PV intolerant or resistant to HU

High-risk P Vera patients intolerant or resistant to hydroxycarbamide (HC)



*in common with the RESPONSE trials patients could receive HC on the BAT arm

BAT (n=87) RUXO (n=93)

Primary outcome

Complete response per ELN (WBC ≤10, HCT ≤0.45, Plt ≤400) rate within 1 year.

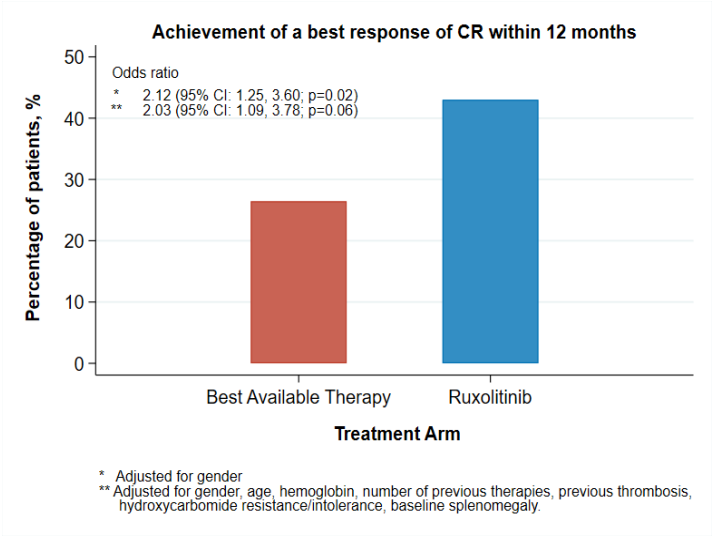
Secondary outcomes

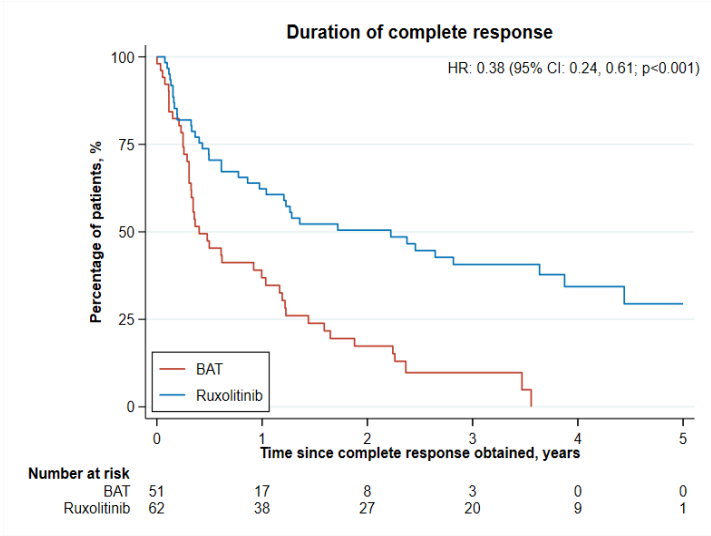
Duration of complete response
Haemorrhagic and thromboembolic event rates
Progression free and overall survival
Responses (Histological, Molecular)
Quality of life and disease symptom burden
Safety and toxicity

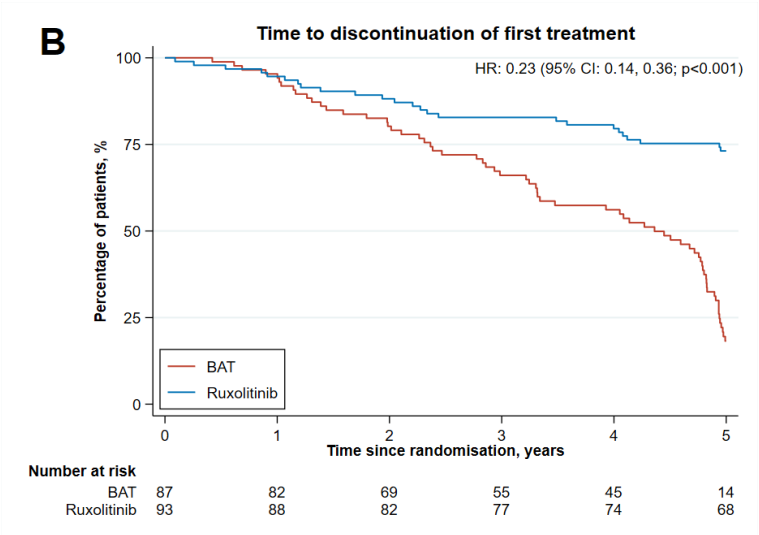
- Ruxolitinib is approved for HC resistant/intolerant PV but trials included cross-over of the control arm limiting knowledge of benefits over longer term clinically-relevant events.

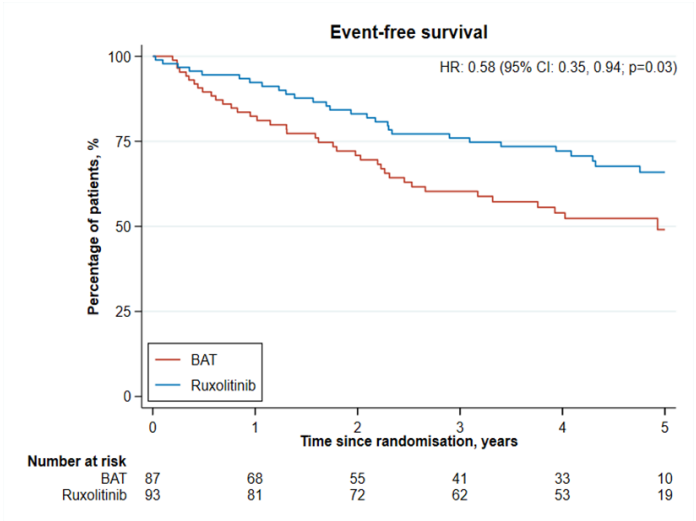
Harrison et al. ASH 2022

Ruxolitinib superior to BAT for CR, duration of CR, time to discontinuation and Event-Free-Survival (thrombosis, haemorrhage, transformation, death)





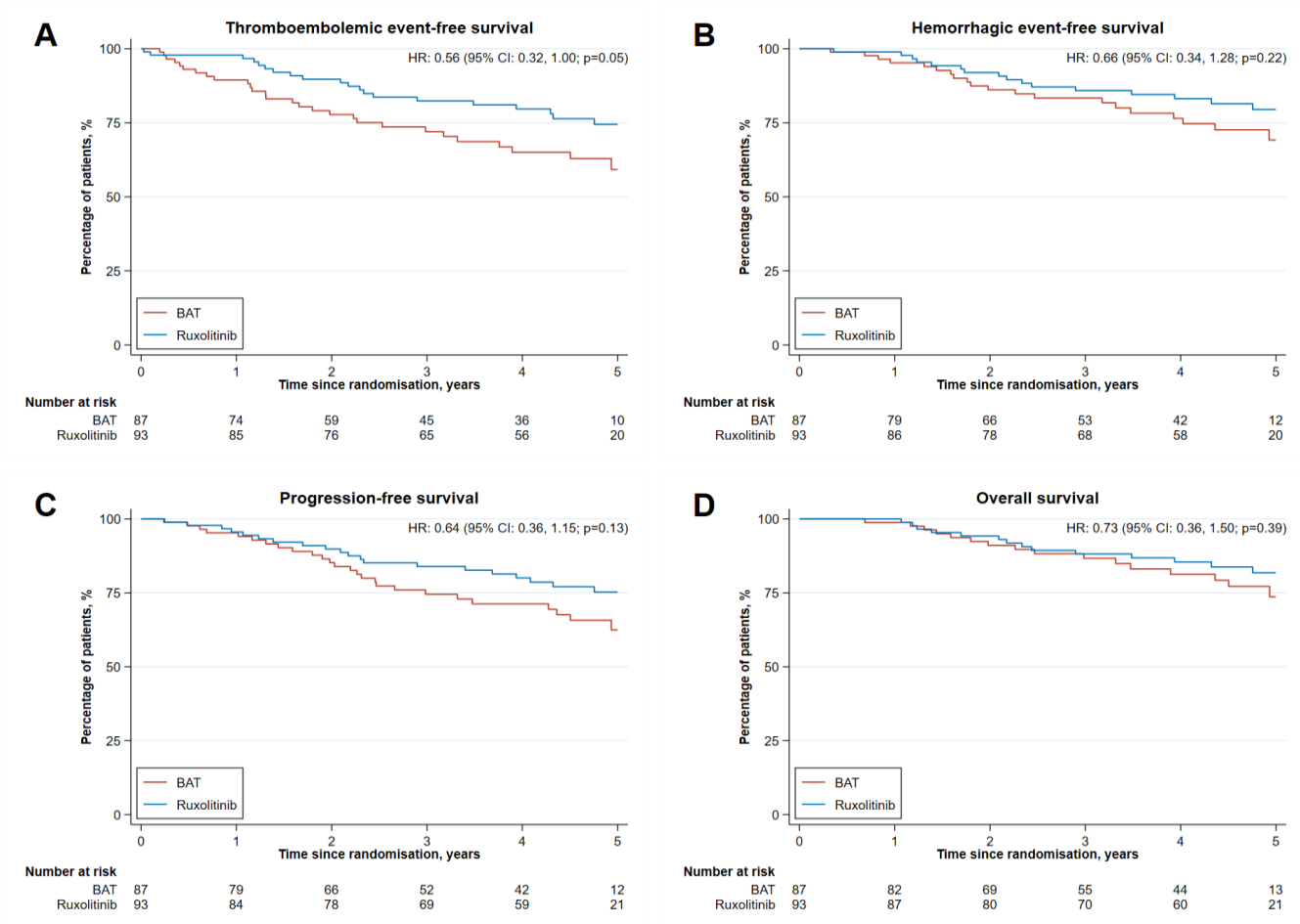




Harrison et al. ASH 2022

Individual clinical endpoints by assigned treatment

Thromboembolic-free-survival
was improved with
ruxolitinib (p=0.05)



Harrison et al. ASH 2022

Conclusions

- La resistenza/intolleranza dell'HU deve essere identificata precocemente.
- Ropeg-interferone ha un effetto sul clone e un effetto sulla sopravvivanza libera da eventi
- Ruxolitinib è stato ampliamento studiato con un effetto sulla malattia, sulla carica allelica nel lungo termine e sulla trombosi.