



DECIMA GIORNATA FIORENTINA DEDICATA AI PAZIENTI
CON MALATTIE MIELOPROLIFERATIVE CRONICHE

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UNIVERSITÀ DEGLI STUDI
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Sistema Socio Sanitario



Regione
Lombardia

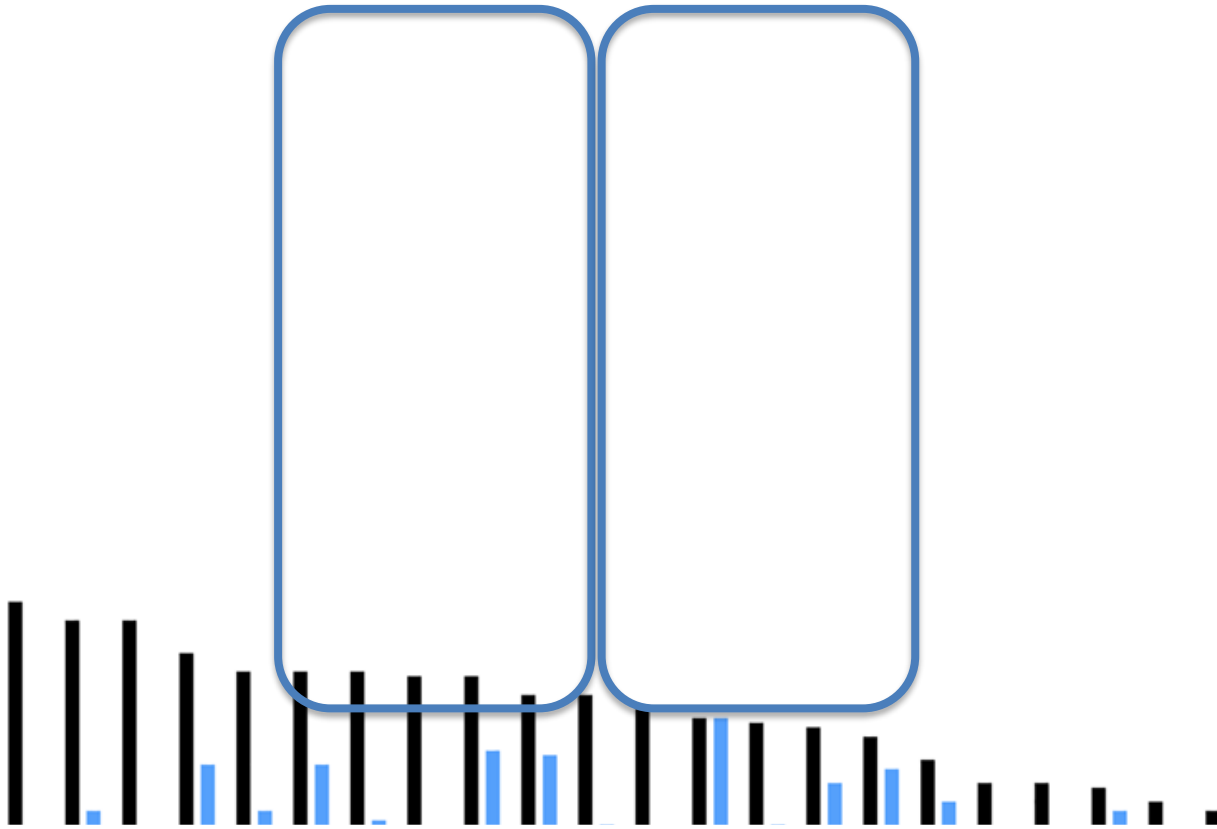
Quando bisogna pensare ad una seconda linea: (ELN 2022): raccomandato

- 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

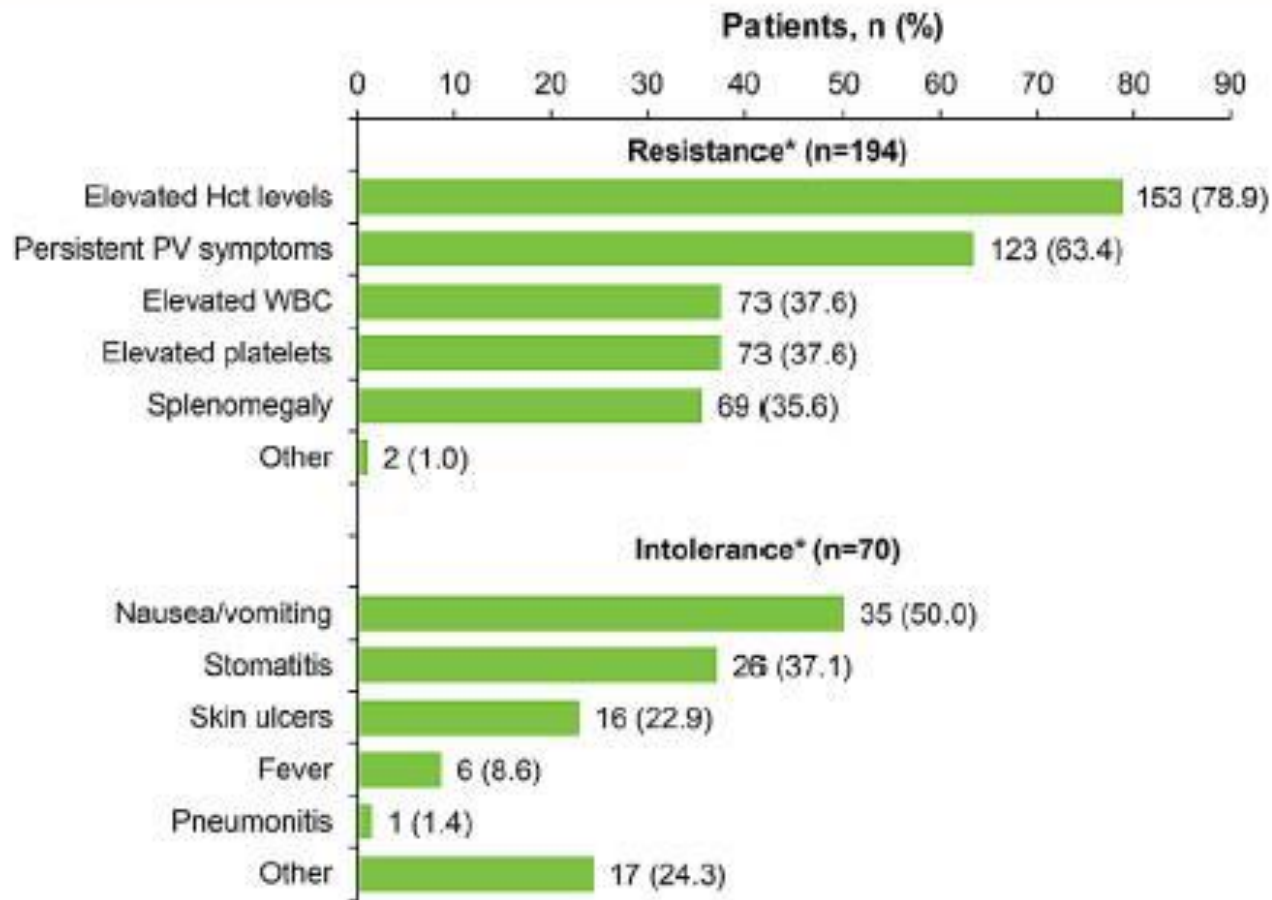
Quando bisogna pensare ad una seconda linea: (ELN 2022): da considerare

- Trombocitosi persistente con $PLT > 1$ milione/ 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

Treatment choice in 1440 patients with PV



Cause di cambio terapia da HU a RUX

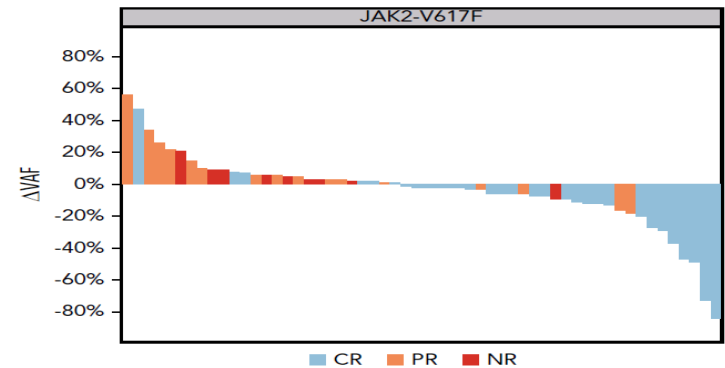
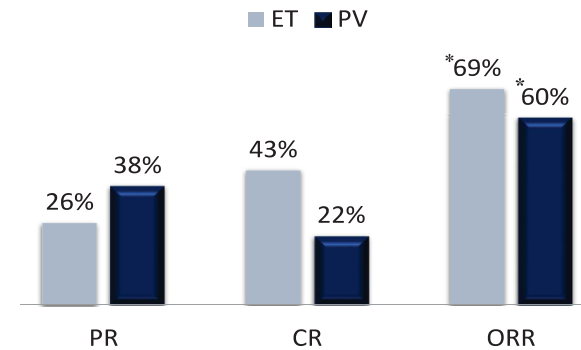


1-year results of Peg-interferon- α 2a as second-line therapy in 50 HR PV: the MPD-RC 111 phase 2 study

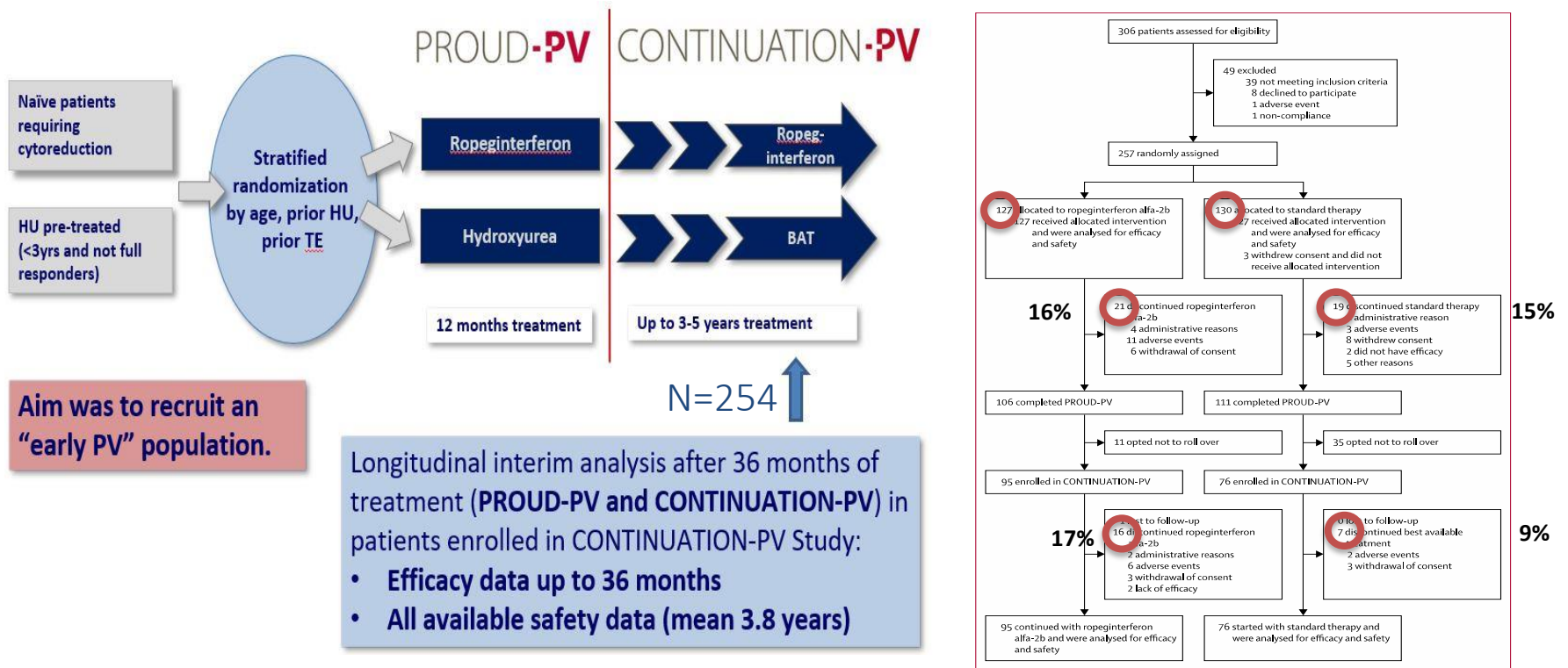
CR means:

- PLT $<400 \times 10^9/L$, WBC $<10 \times 10^9/L$
- 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%



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



PROUD/CONTINUATION-PV: baseline characteristics

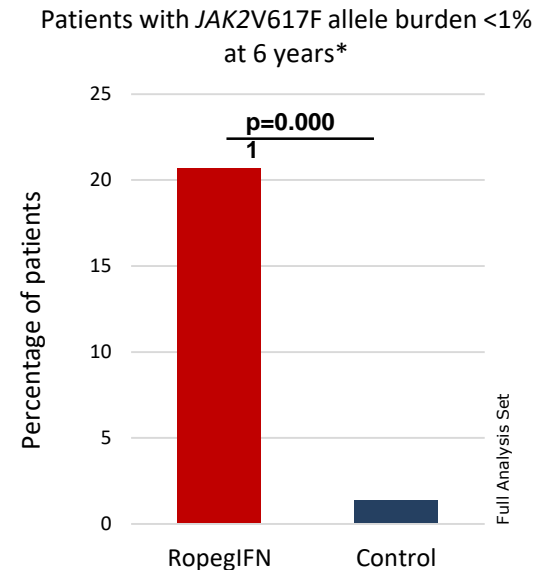
	PROUD-PV		CONTINUATION-PV*	
	Ropeginterferon alfa-2b (n=127)	Hydroxyurea (n=127)	Ropeginterferon alfa-2b (n=95)	Best available treatment (n=76)
Female	68 (54%)	67 (53%)	48 (51%)	40 (53%)
Male	59 (46%)	60 (47%)	47 (49%)	36 (47%)
Age, years				
Median	60.0 (52.0-66.0)	60.0 (48.0-67.0)	58.0 (50.0-64.0)	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

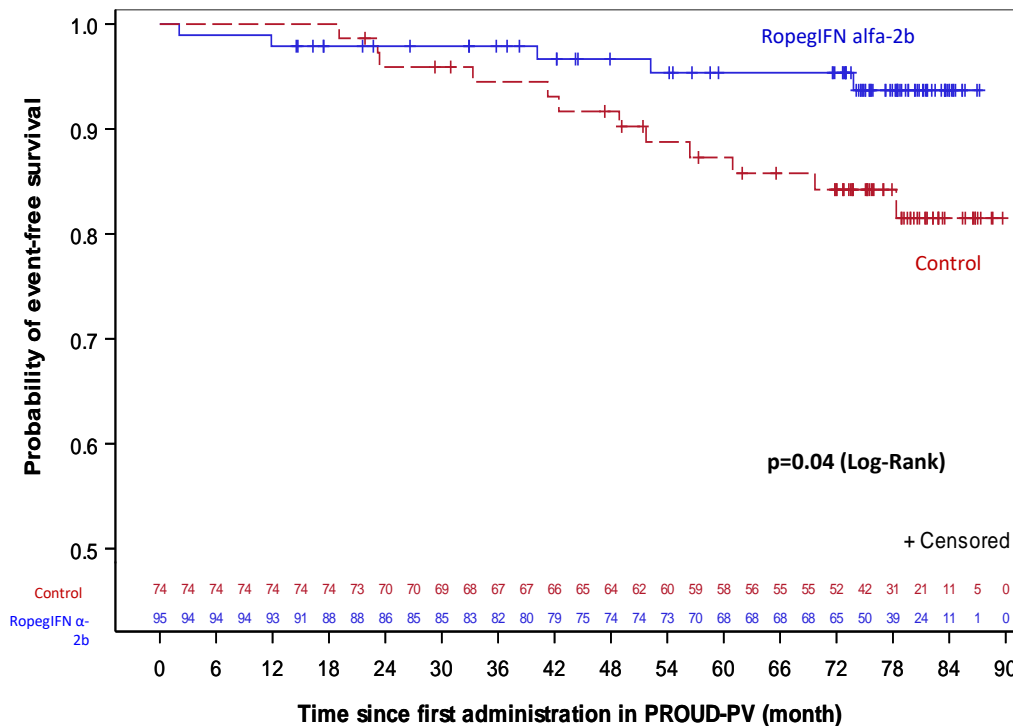
- After 6 years of treatment, the *JAK2* V617F allele burden decreased to <1% in 20.7% of patients in the ropeginterferon alfa-2b arm.
- In contrast, only 1.4% of patients in the control arm achieved an allele burden <1% at 6 years of treatment ($p=0.0001$).



*Analyzed in patients with baseline allele burden >10%; last observation carried forward

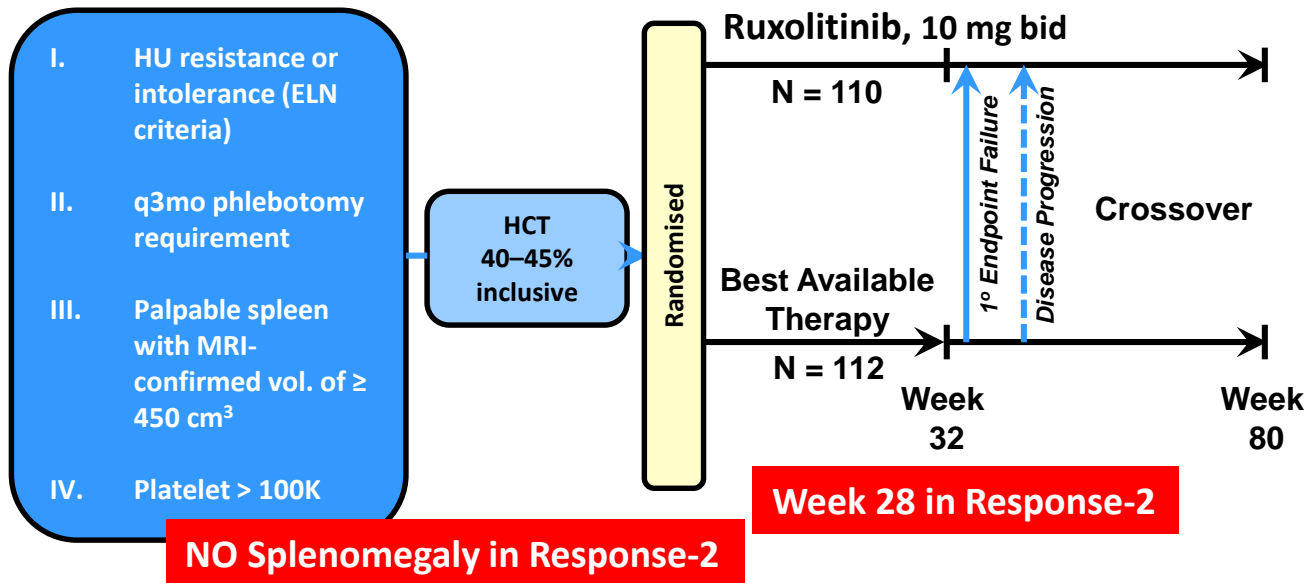
PROUD/CONTINUATION-PV: Event-free survival

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)

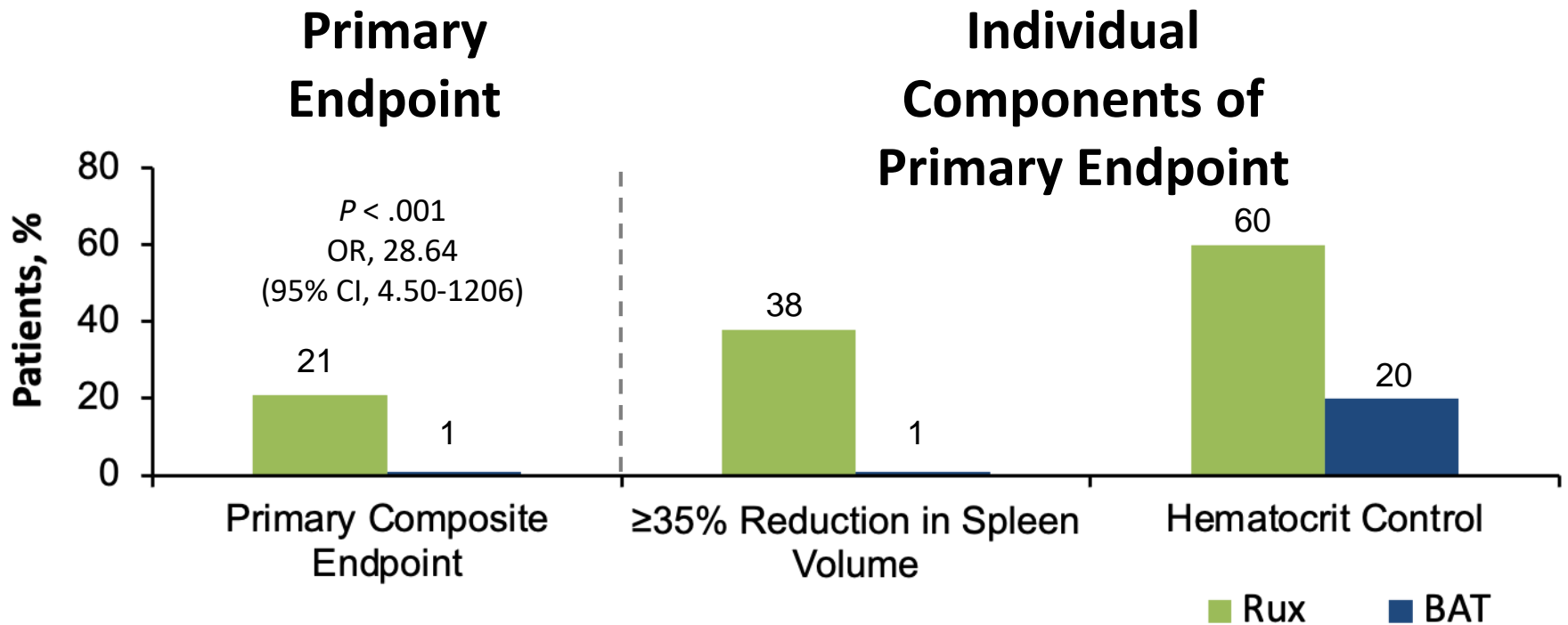
Ruxolitinib as 2nd line in PV: the Response trials



- 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)

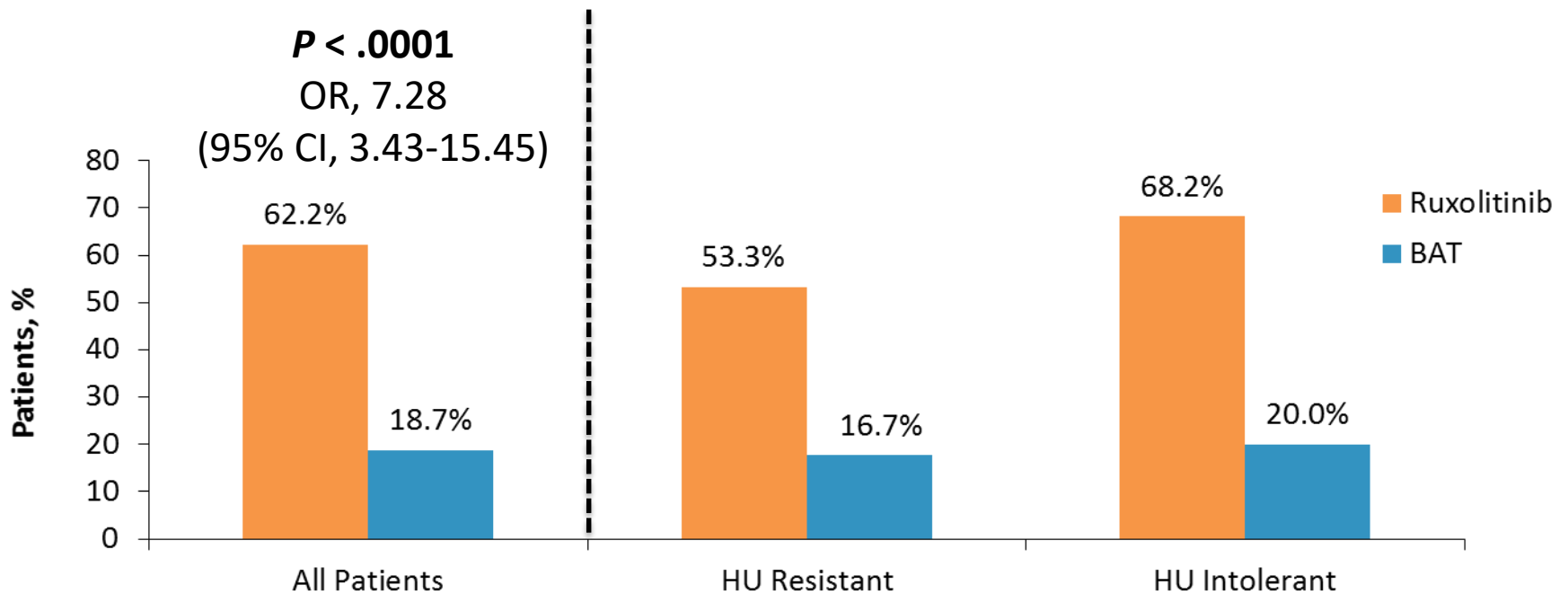
RUX induce il controllo HCT senza flebotomia e SVR35 nel 21% dei pazienti PV che hanno fallito HU

The RESPONSE trial



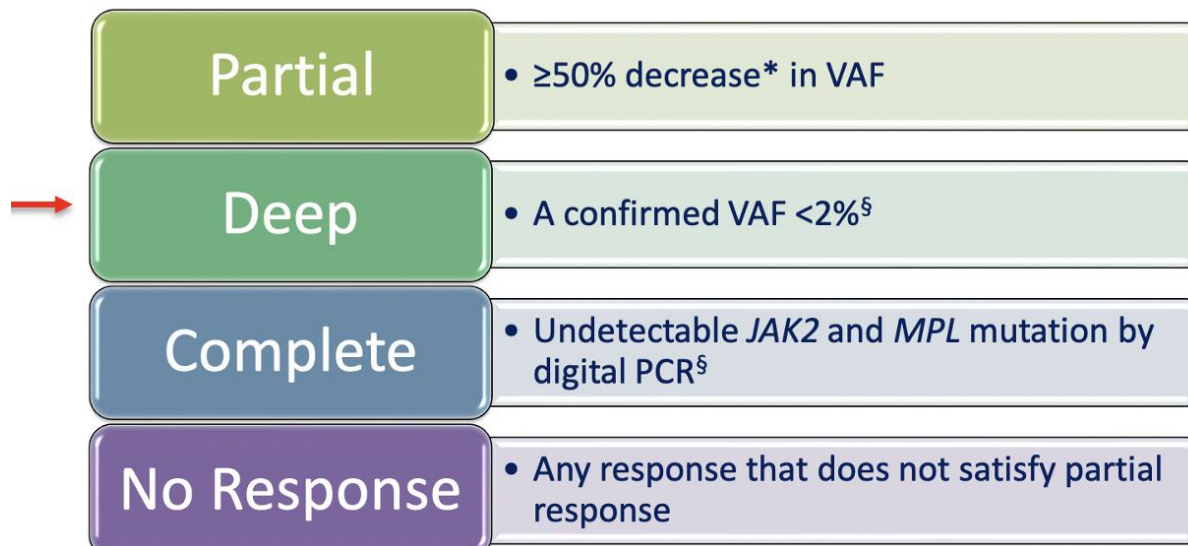
RUX induce il controllo dell'HCT senza flebotomia nel 62% dei pazienti PV che hanno fallito l'HU senza splenomegalia

RESPONSE-2 trial

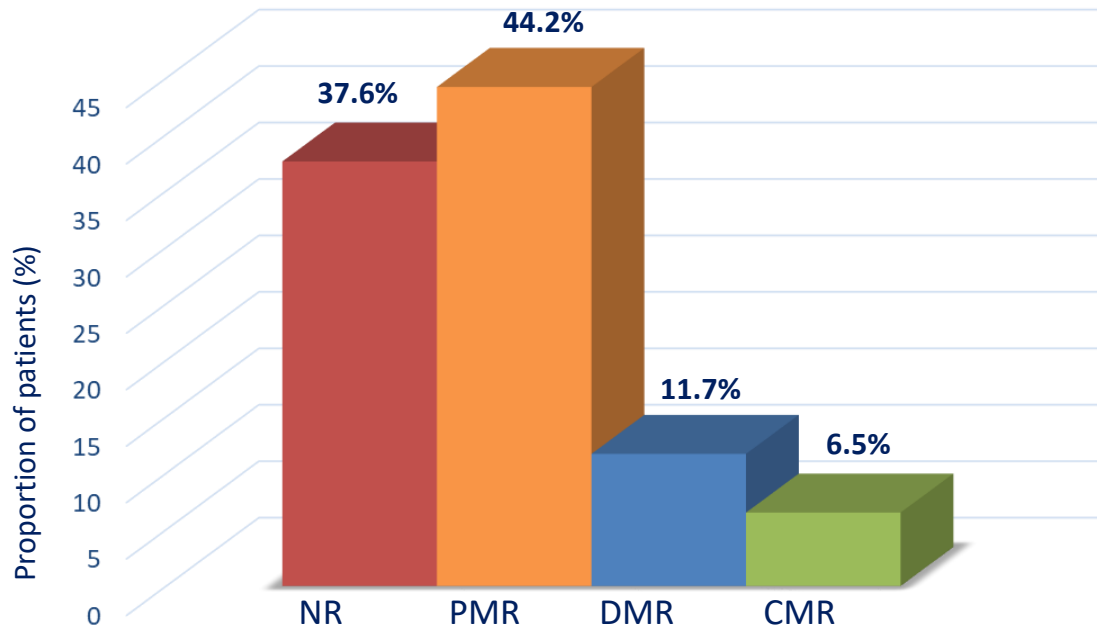


Risposta molecolare di JAK2 in pazienti con PV & ET trattati con RUX

- 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

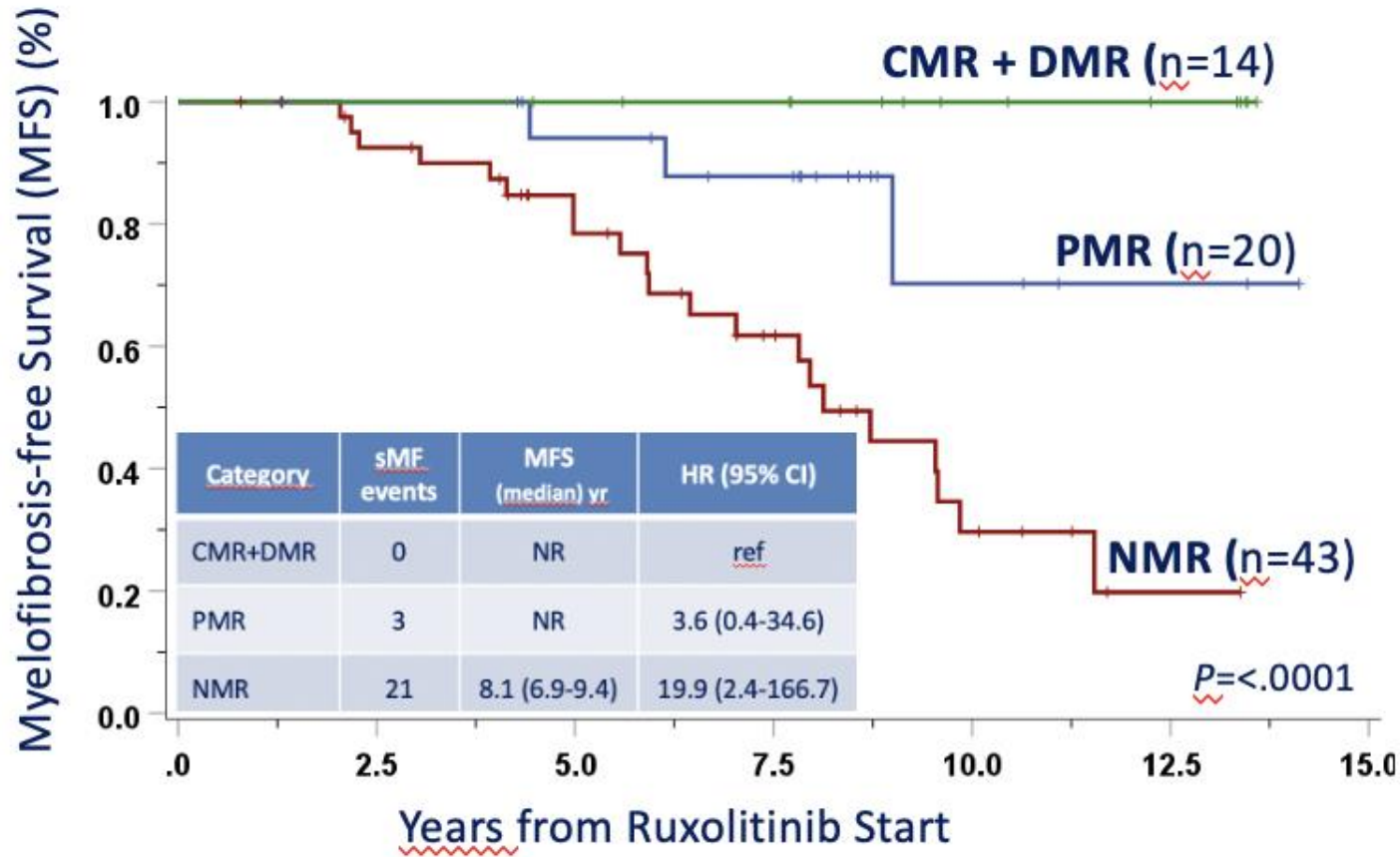


Risposta molecolare di JAK2 V617F in PV & ET



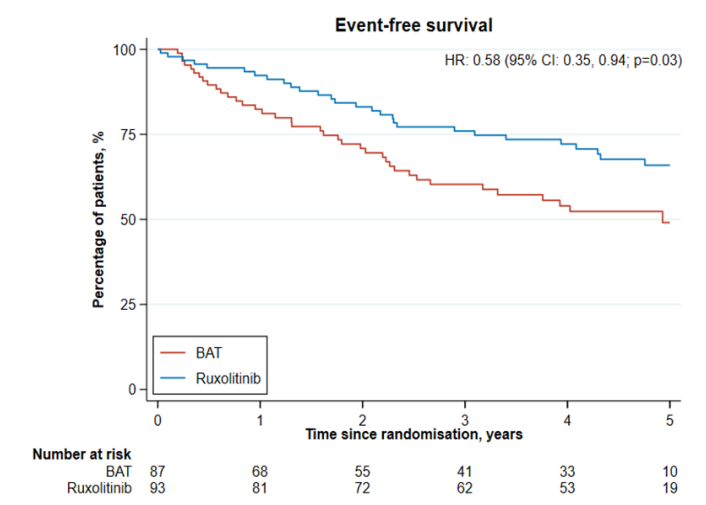
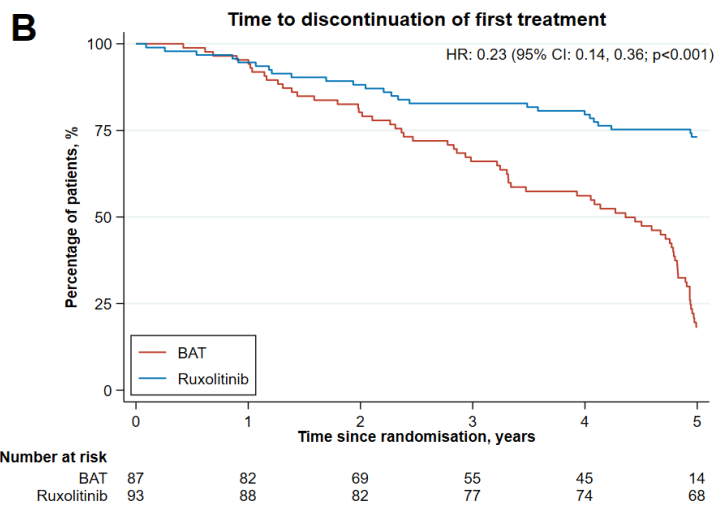
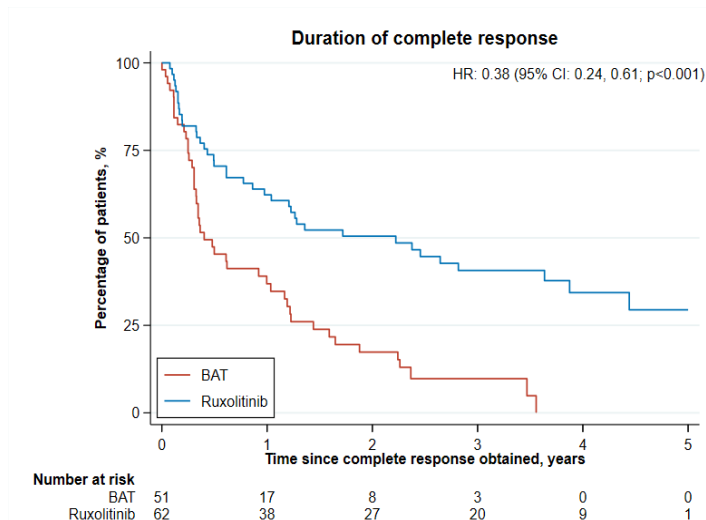
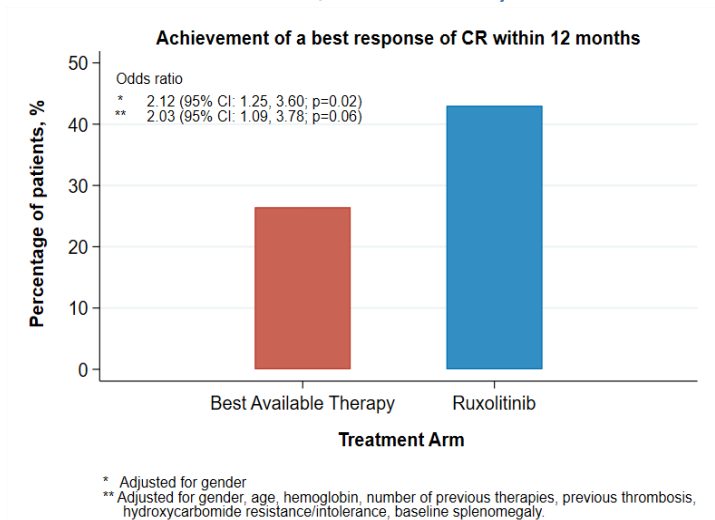
- Il tempo mediano a CMR e DMR è stato di 4,6 anni (1,1-7,6 anni) e 5,0 anni (2,1-12,1 anni).

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



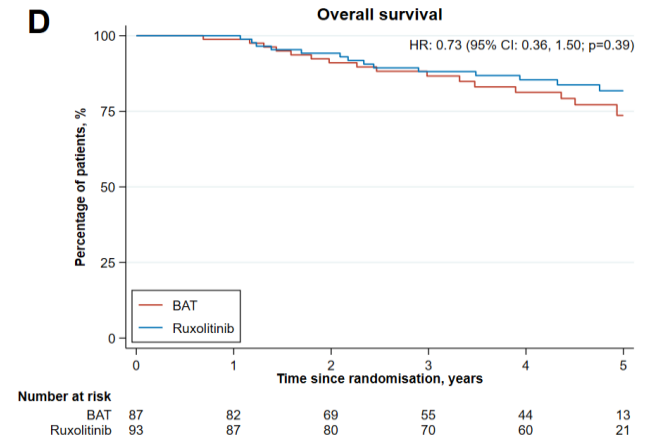
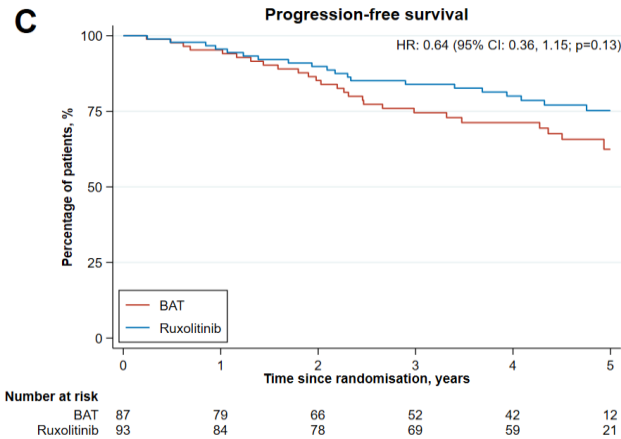
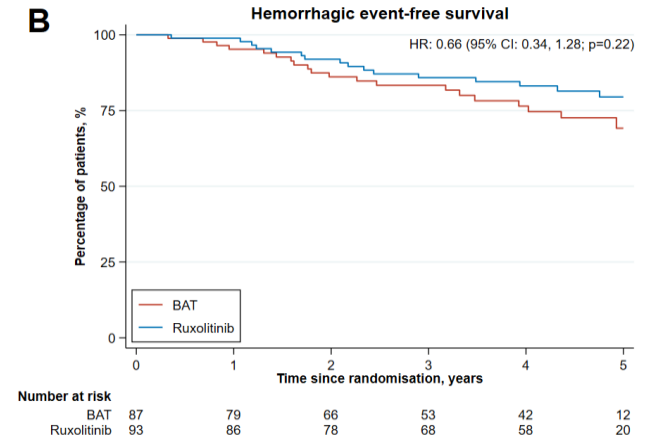
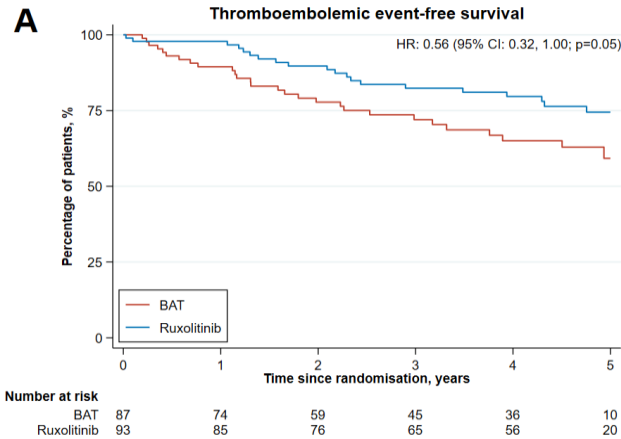
- 24 patients (31.1%) progressed to sMF after a median of 6.0y (2-11.5). 34% were PV and 16.6% ET.

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

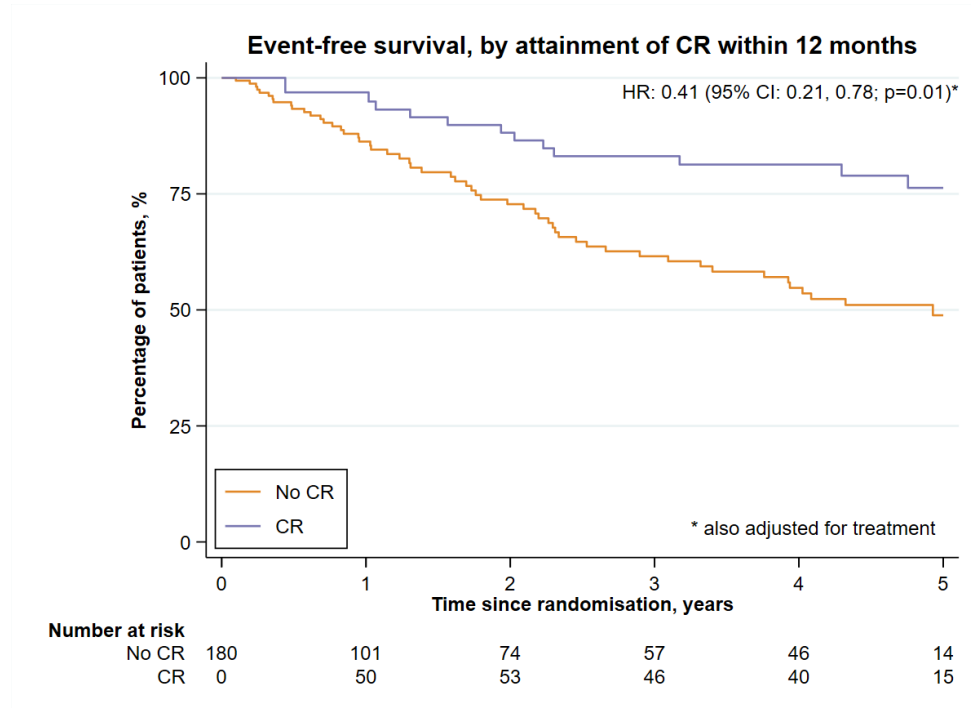
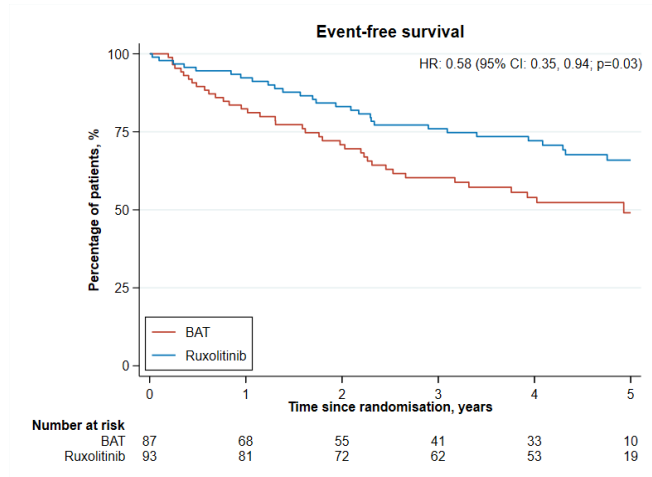


Individual clinical endpoints by assigned treatment

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

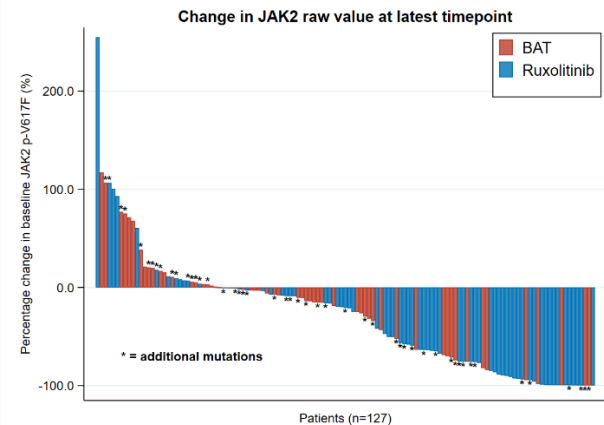


EFS (major haemorrhage, thrombosis, transformation or death) was superior for RUX & for attaining a CR within 1 yr



Molecular analyses

- Median baseline JAK2V617F VAF did not differ 64% (RUX), 58% (BAT)
- @12m:
 - >25% reduction in 32% RUX and 30% BAT
 - >50% reduction in 14% RUX and 18% BAT
- @final evaluable time-point:
 - >50% reduction in 56% RUX and 25% BAT
- Median time to mol response was 36 months for RUX
- Molecular response at 1 year correlated with superior EFS
- Those with durable molecular response at last time point had significant improvements in EFS, PFS and OS regardless of treatment arm



Conclusions

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