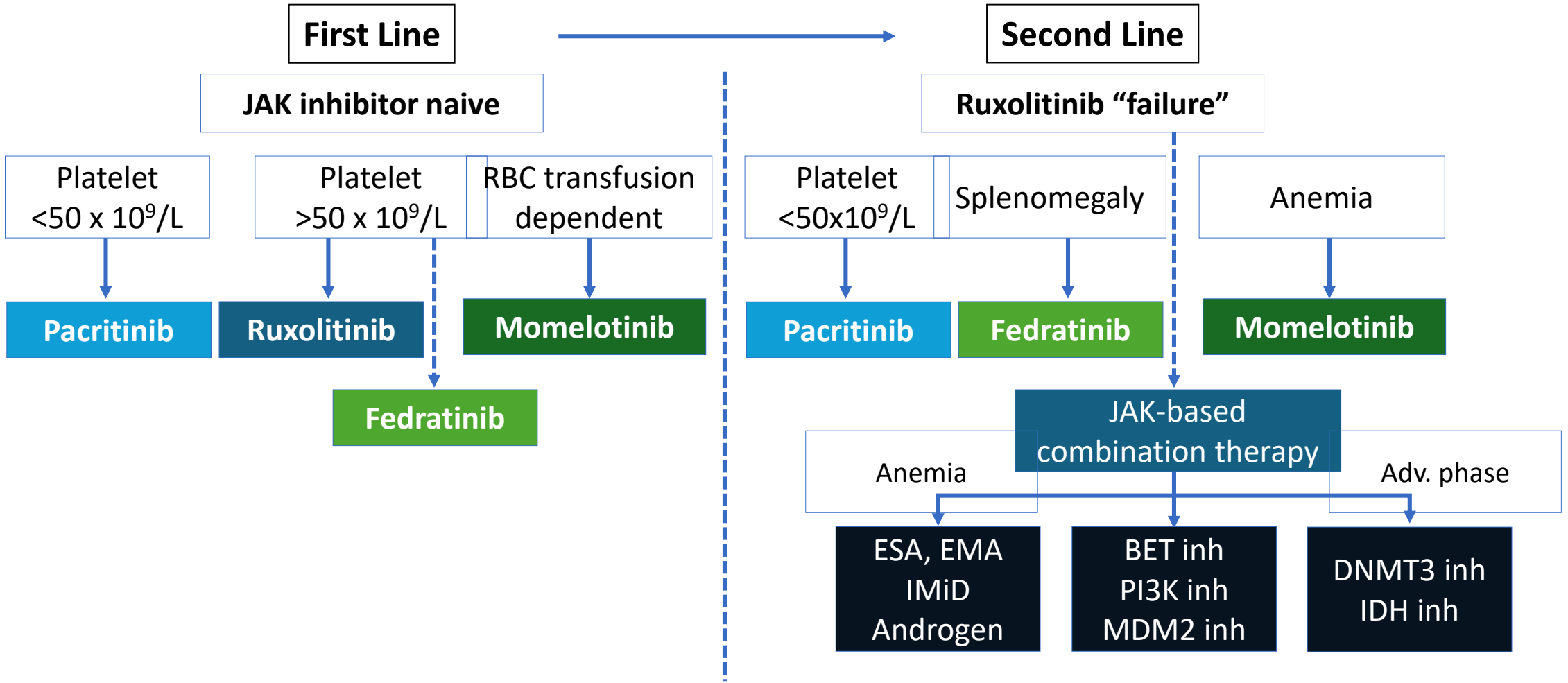
DECIMA GIORNATA FIORENTINA DEDICATA AI PAZIENTI
CON MALATTIE MIELOPROLIFERATIVE CRONICHE

Aula GIALLA

JAK2 inibitori: vecchi e nuovi

Massimo Breccia

Quanti JAK Inibitori abbiamo?



Venugopal. J Hematol Oncol. 2020;13:162.

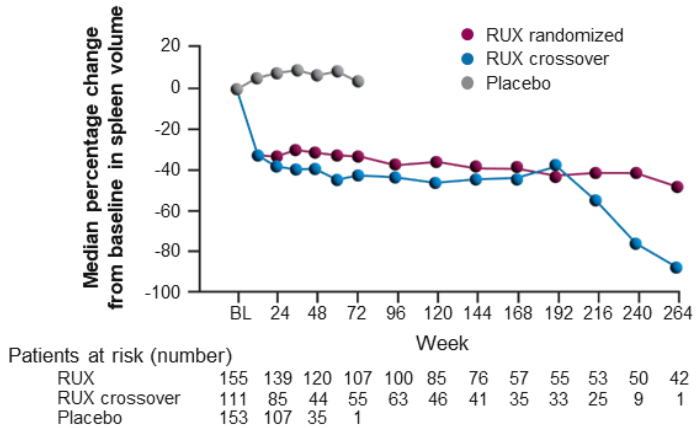
Quali sono i vantaggi di Ruxolitinib nella Mielofibrosi?

Splenomegalia

Evidence of therapeutic benefit based on SVR35[1-4]

COMFORT-I Study: Randomized, double-blind, placebo-controlled, phase 3 study | 5-year analysis | n=309

[3,4]



Among patients originally randomized to RUX, 59.4% (92/155) achieved a ≥ 35% reduction in spleen volume at any time during the study

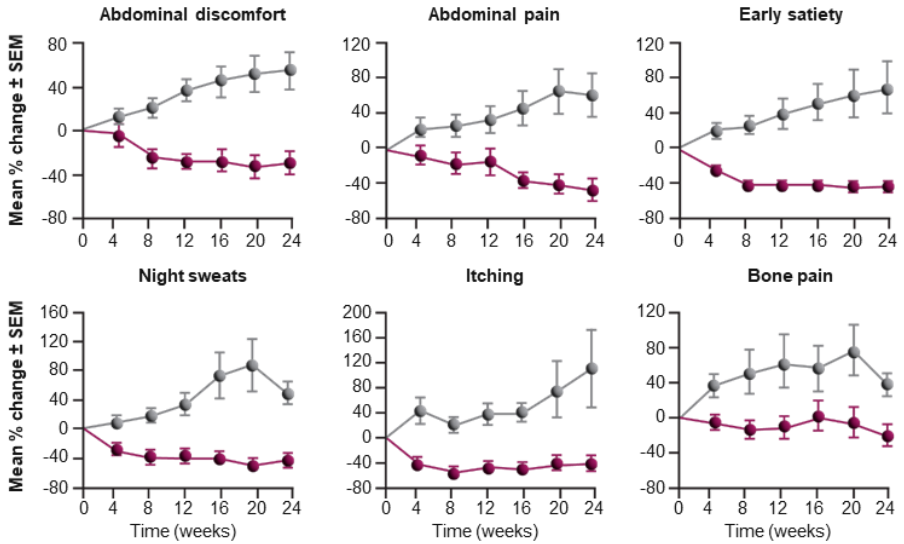
50% of patients maintained the response at 5 years[3]

Simptomi

Evidence of therapeutic benefit based on TSS50[1,2,4]

COMFORT-I Study

[4,5]



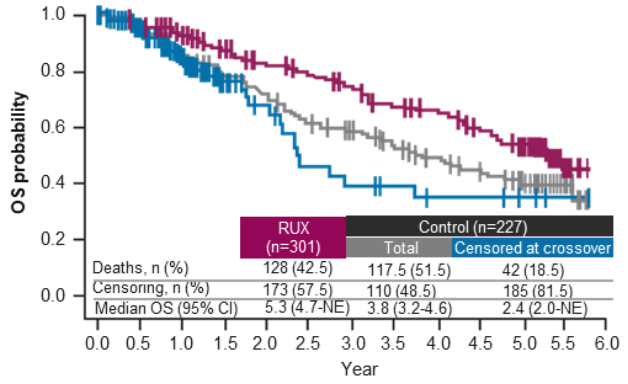
Individual symptom scores, as assessed by the modified MFSAF v2.0 at each 4-week timepoint in patients receiving RUX, showed **improvement relative to baseline[4]**

Sopravvivenza

Some evidence of survival benefit for ruxolitinib[1-3]

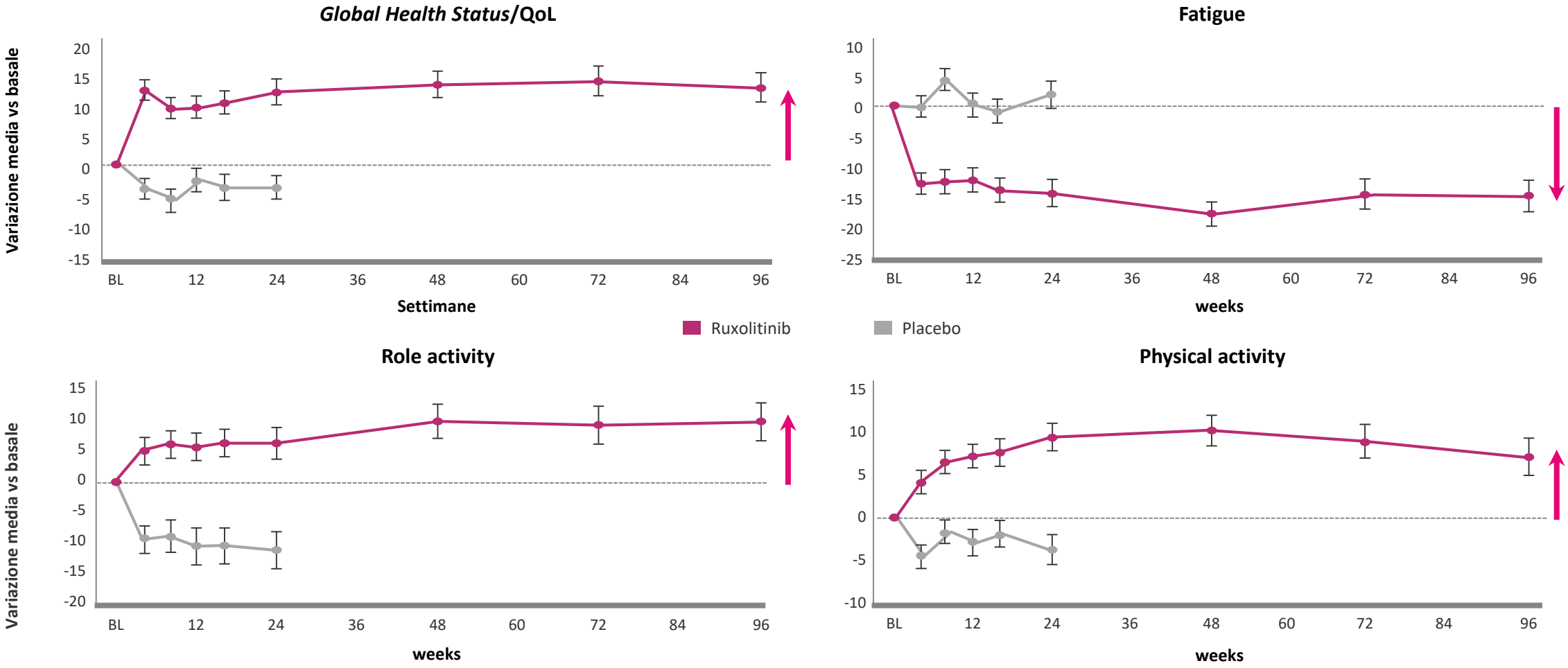
COMFORT I and COMFORT-II Studies (Randomized, open-label, active-controlled, phase 3 study with crossover) | 5-year pooled analysis of overall survival

[6,7]



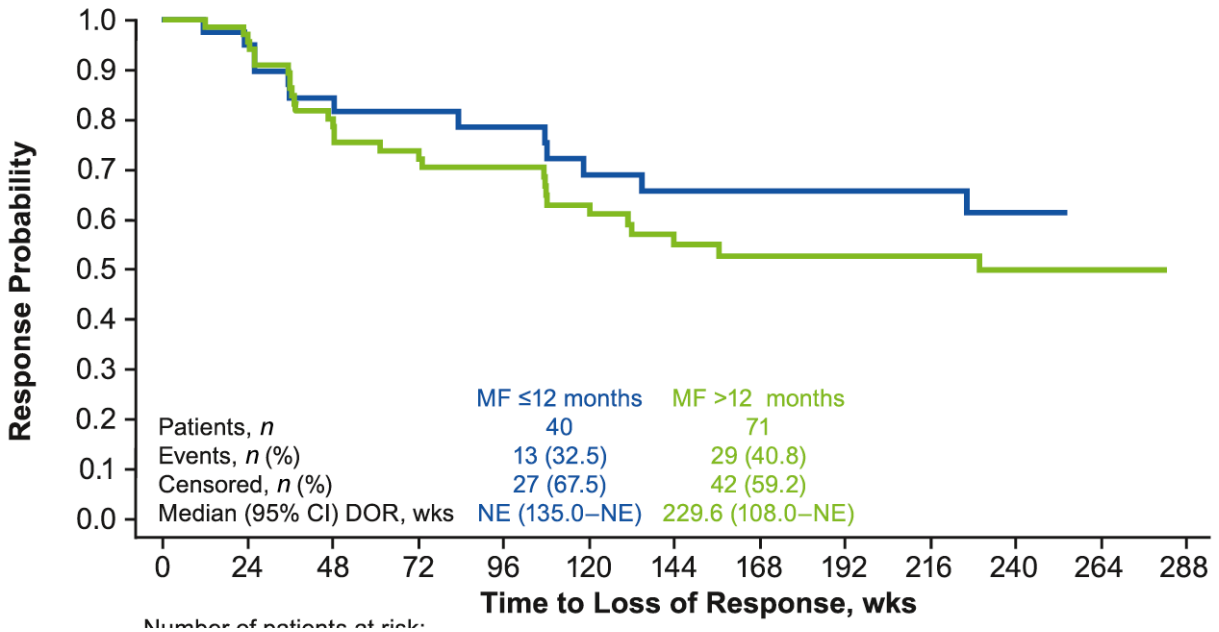
- MFSAF, myelofibrosis symptom assessment form; RUX, ruxolitinib; SVR35, ≥35% spleen volume reduction from baseline; TSS50, ≥50% improvement in Total Symptom Score from baseline.
- [1] JAKAFI (ruxolitinib). U.S. Prescribing Information. January 2023. [2] JAKAVI (ruxolitinib). Summary of Product Characteristics. May 2022. [3] Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55. [4] ClinicalTrials.gov COntrolled MyeloFibrosis Study With ORal JAK Inhibitor Treatment: The COMFORT-I Trial. Available at: https://clinicaltrials.gov/ct2/show/NCT00952289. Accessed June 2, 2023. [5] Mesa RA, et al. *J Clin Oncol*. 2013;31(10):1285-1292. [6] Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):156. [7] ClinicalTrials.gov Controlled Myelofibrosis Study With Oral Janus-associated Kinase (JAK) Inhibitor Treatment-II: The COMFORT-II Trial. Available at: https://clinicaltrials.gov/ct2/show/NCT00934544. Accessed June 2, 2023.

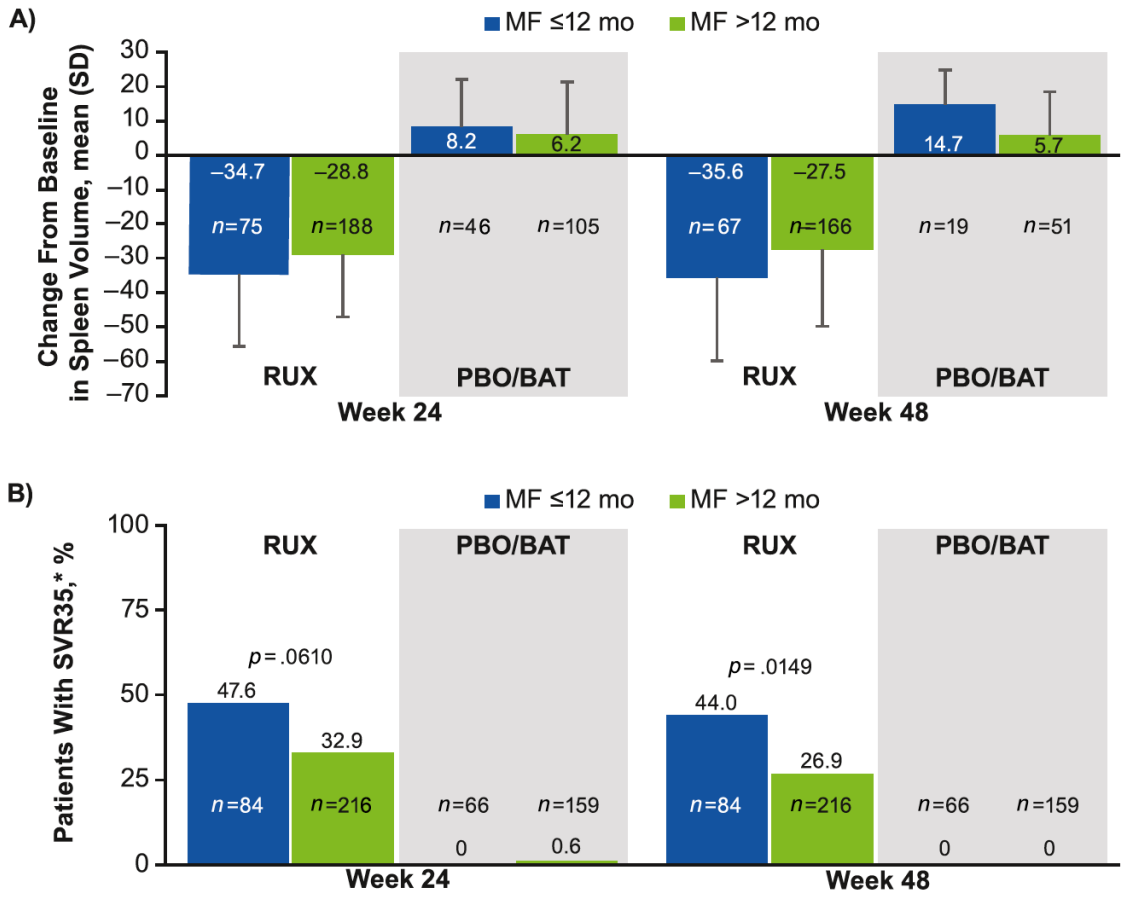
La Qualità di vita migliora e si mantiene nel tempo



1. Verstovsek S, et al. Haematologica 2013; 98(12): 1865-71.

Se si inizia prima la risposta splenica è migliore

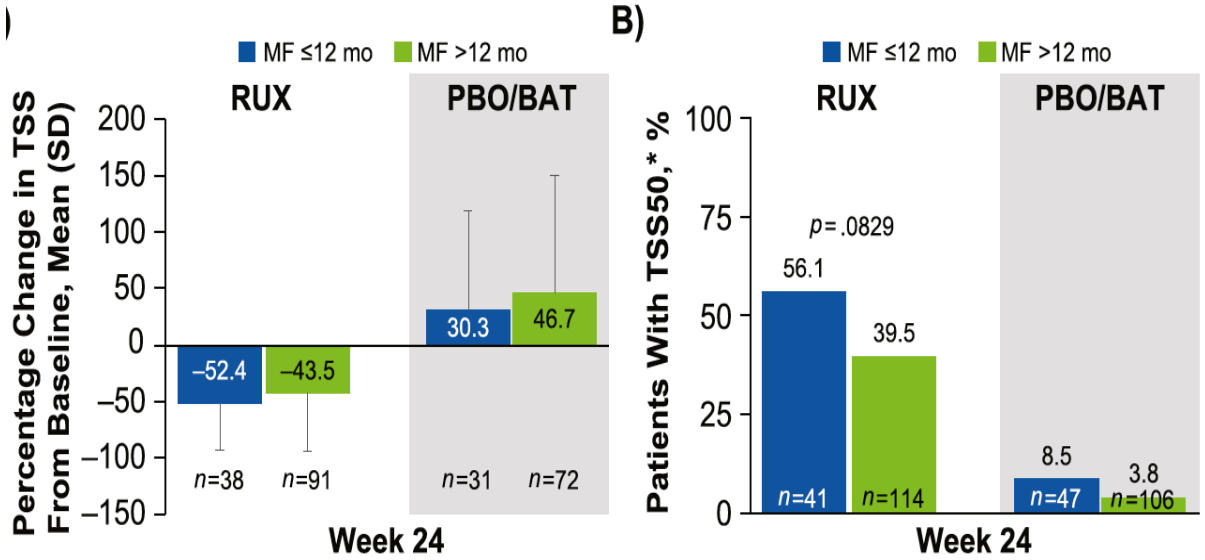


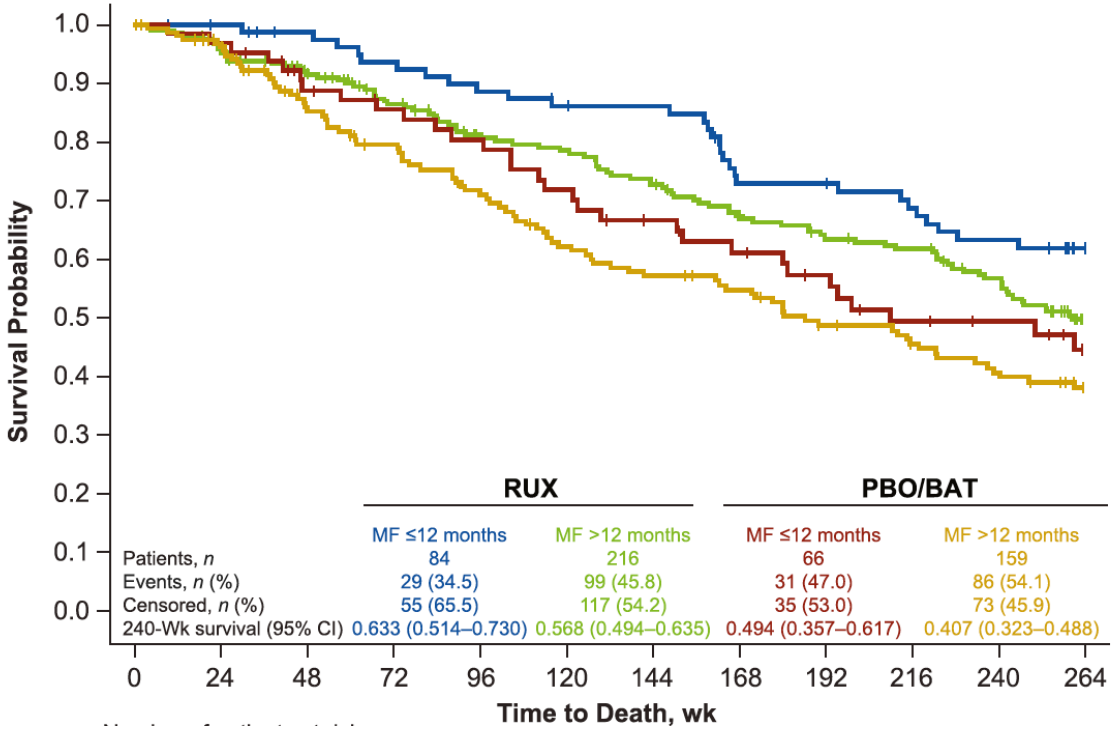


- 84 hanno ricevuto ruxo <12 mesi e 216 dopo 12 mesi
- **Sono state osservate meno anemia e trombocitopenia nei pazienti che hanno iniziato precocemente**
- La SVR era più alta per i pazienti che avevano iniziato ruxolitinib prima (47,6% vs. 32,9% alla settimana 24, p = 0,0610; 44,0% vs. 26,9% alla settimana 48, p = 0,0149).

Verstovsek et al Cancer 2023.

Se si inizia prima anche i sintomi migliorano prima

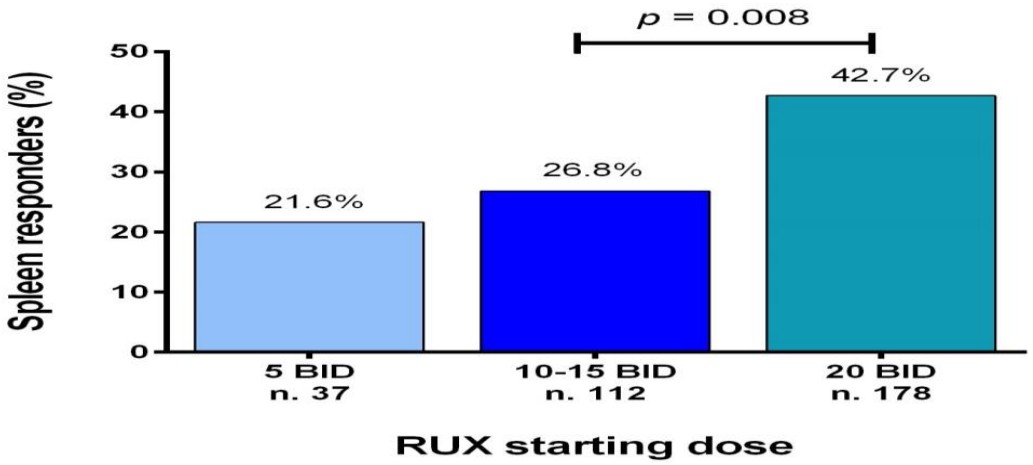


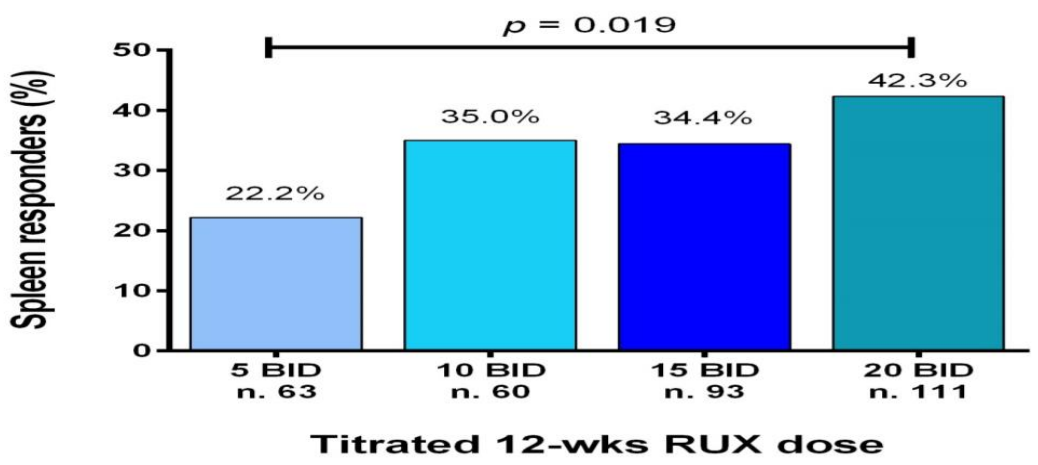


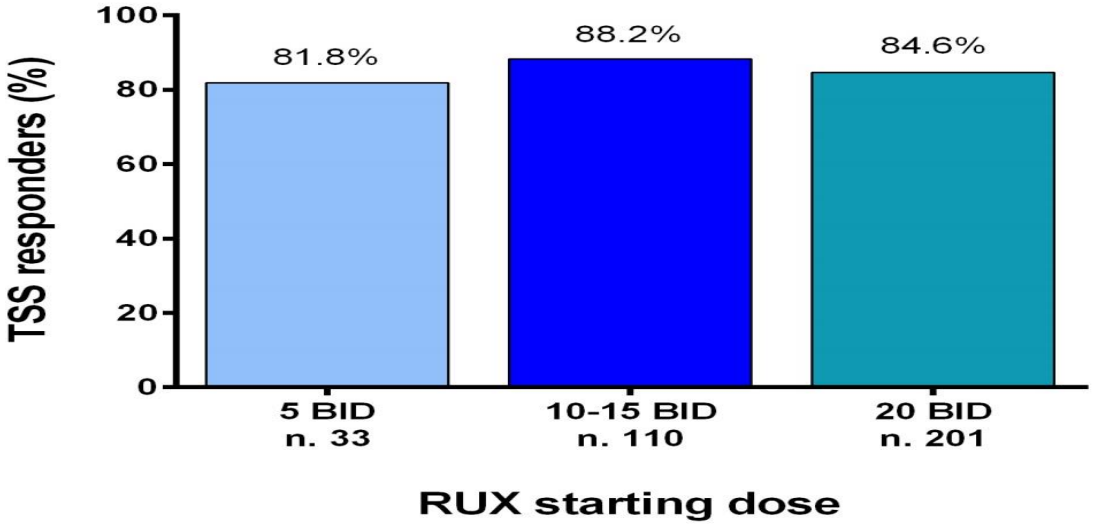
- 525 pz inclusi (84 hanno ricevuto ruxo <12 mesi e 216 dopo 12 mesi)
- Alla settimana 240, **l'OS era significativamente migliorata tra i pazienti che avevano iniziato ruxolitinib prima** (63% [IC 95%, 51%-73%] vs. 57% [IC 95%, 49%-64%]

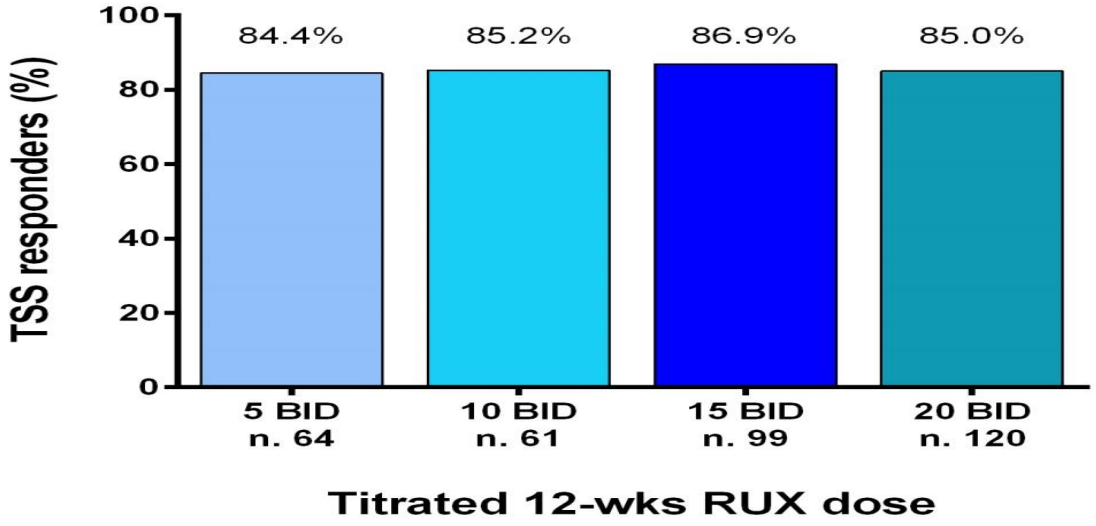
Verstovsek et al Cancer 2023.

La dose iniziale e il mantenimento di questa si associa a risposte migliori





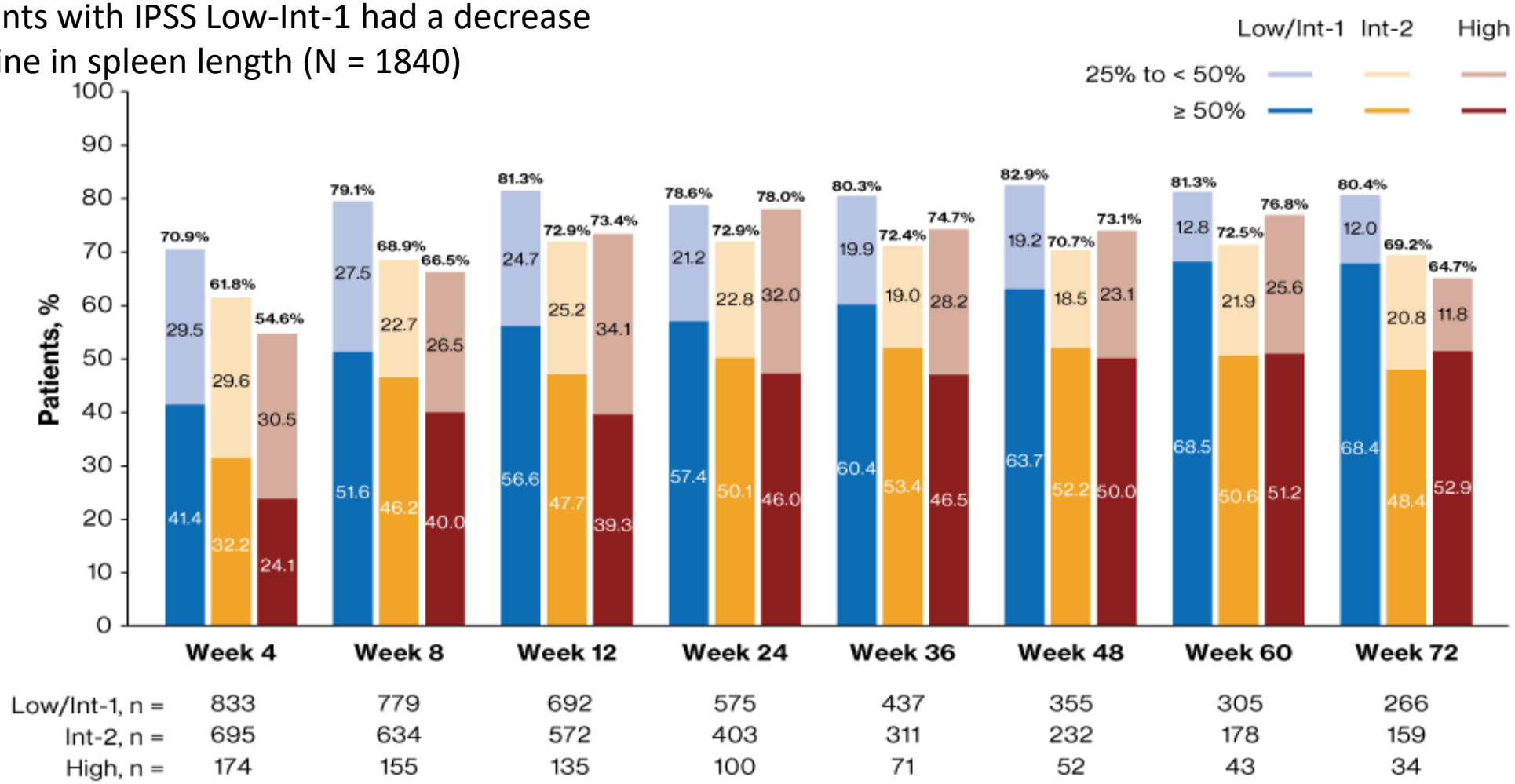




Palandri F, et al. *Oncotarget.* 2017. doi:10.18632/oncotarget.18674.

Studio JUMP: risposte spleniche anche nei pazienti con rischio inferiore

More patients with IPSS Low-Int-1 had a decrease from baseline in spleen length (N = 1840)



From Passamonti F *et al*, EHA; 2017; [Abs E1333].

Meno tossicità nei pazienti a rischio intermedio-1

Main Hematologic AEs G3-4	Low/Int-1 (N=893)	Int-2 (N=754)	High (N=193)
Anemia	22%	44%	55%
Thrombocytopenia	11%	18%	25%
Neutropenia	4%	5%	7%
Leukocytosis	1%	1%	7%
Main Non-Hematologic AEs G3-4			
Pneumonia	3%	5%	9%
Urinary Tract Infection	1%	1%	3%

Primary reason for discontinuation	Low/Int-1 (N=893)	Int-2 (N=754)	High (N=193)
AEs	14,9%	17,1%	27,5%
Progression	6,2%	11,1%	11,4%
Death	2,0%	4,8%	10,9%
Physician decision	3,4%	5,6%	1,6%

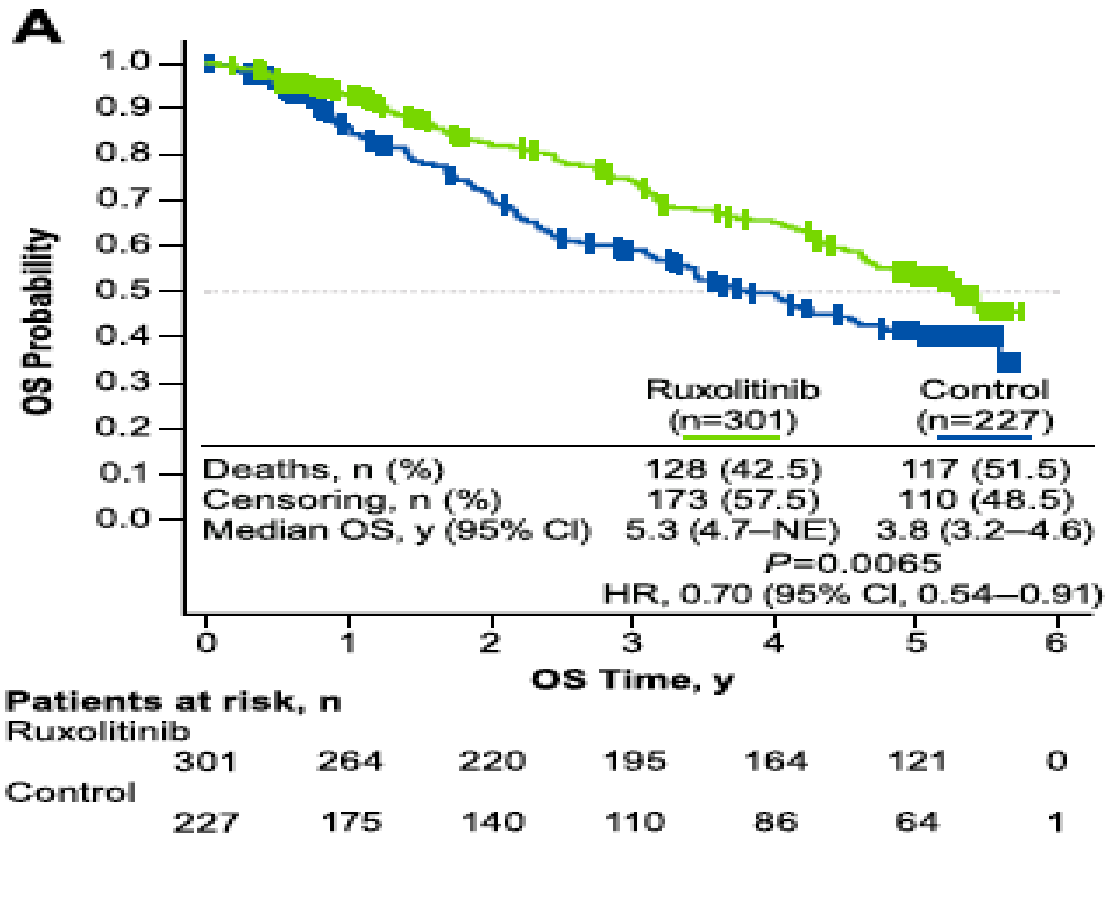
Most common AEs Anemia and Thrombocytopenia.

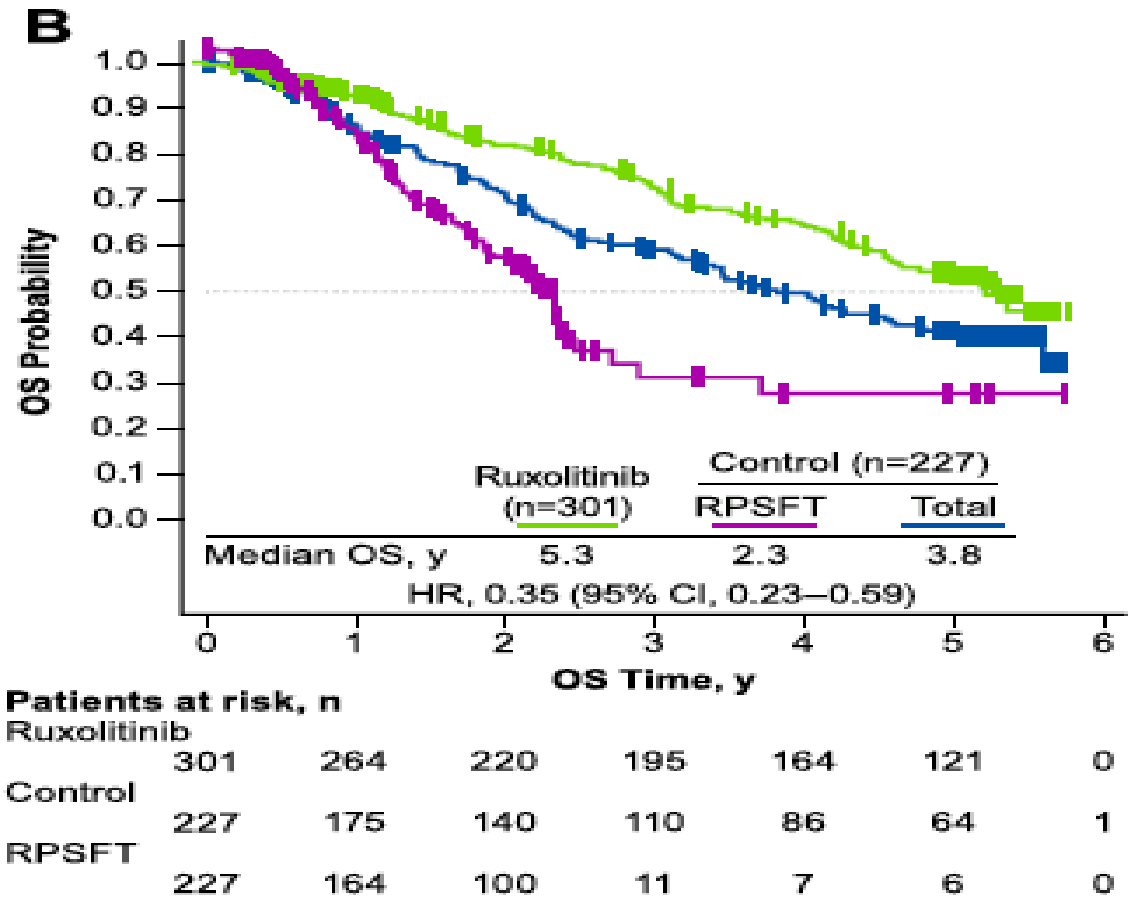
Lower-risk pts had lower rates of hematologic AEs.

AE profile consistent with previous reports.

Passamonti, F. (2017). *Haematologica : The Hematology Journal, 102*, 548; NCT01493414 at ClinicalTrials.gov

Ruxolitinib e sopravvivenza: si riduce il rischio di mortalità

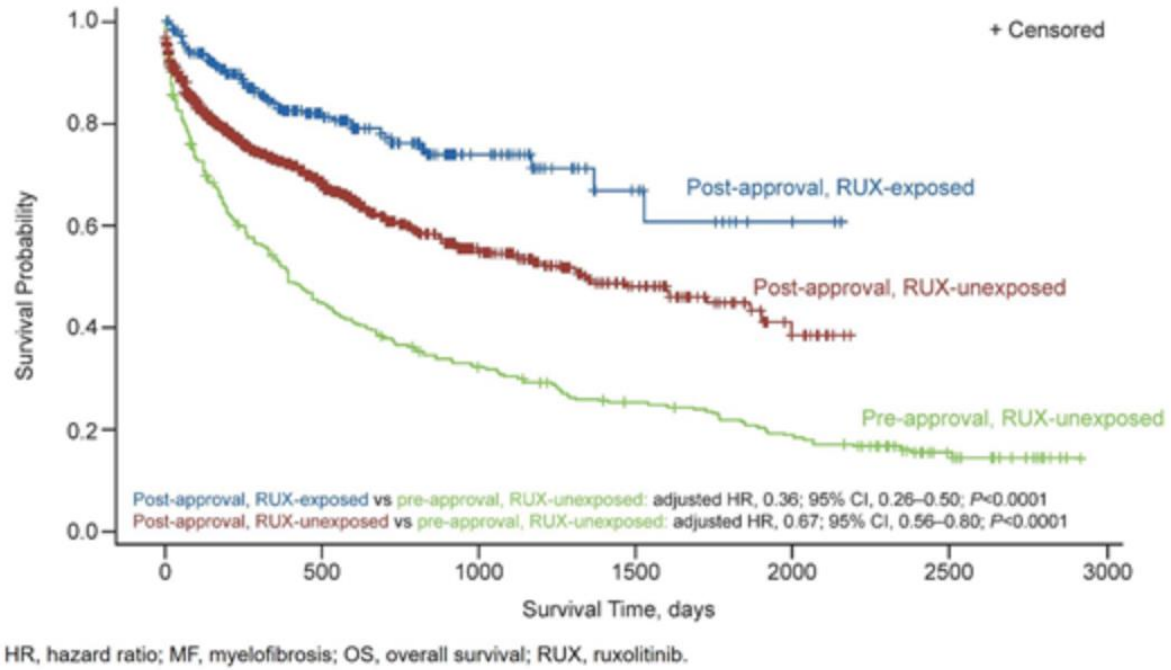




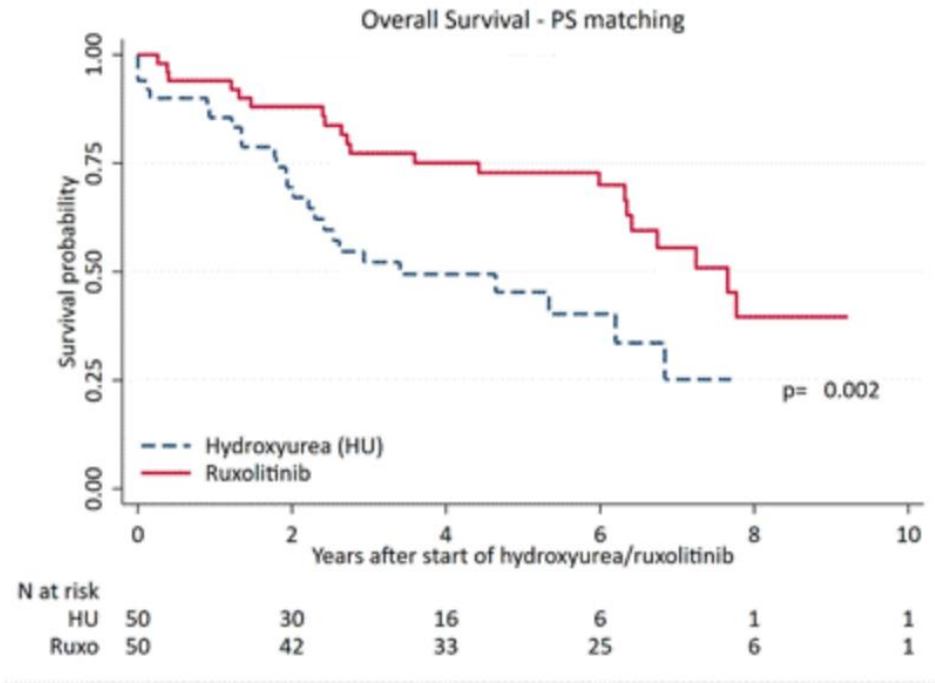
The risk of death was reduced by 30% among patients randomized to ruxolitinib

Verstovsek *et al*; J Hematol Oncol 2017

Anche nella “real-life” vantaggio di sopravvivenza



HR, hazard ratio; MF, myelofibrosis; OS, overall survival; RUX, ruxolitinib.



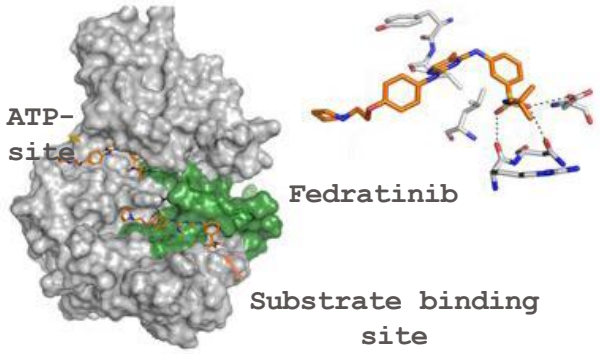
Medi-Care analysis in 1677 MF patients

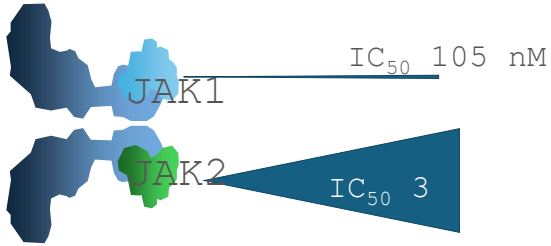
ERNEST project in 1010 MF patients

Verstovsek *et al*; ASH 2020; Guglielmelli et al EHA 2021

Fedratinib

FEDRATINIB is a kinase inhibitor indicated for the treatment of patients with INT-2 or HR MF





- Un inibitore della chinasi orale con attività contro JAK2 e FLT3 attivati mutazionalmente
- Attività inibitoria simile su JAK2 V617F wild type e mutato
- L'inibitore più selettivo di JAK2 con una maggiore attività inibitoria per JAK2 (35 volte maggiore rispetto a JAK1) rispetto ai membri della famiglia JAK1, JAK3 e TYK2 (preservando così la corretta funzione immunitaria)
- L'emivita di Fedratinib (41 ore) consente

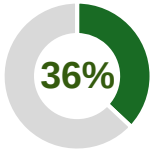
Santos & Verstovsek. Blood Rev 2011

Quali sono i vantaggi di Fedratinib nella Mielofibrosi?

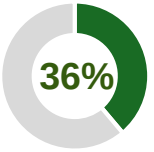
JAKARTA Trial[1,2]

Randomized, double-blind, placebo-controlled, phase 3 study
FED vs placebo in
Int-2/high-risk MF 1st line

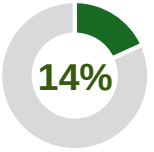
Fedratinib 400 mg



Spleen volume reduction ≥ 35%



Symptom burden reduction ≥ 50%

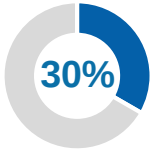


Discontinuation due to AEs

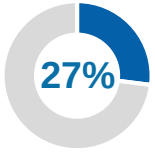
JAKARTA-2 Trial[3-5]

Open label, single arm, phase 2 study
FED in Int-2/high-risk MF 2nd line

Reanalysis (2019)*



Spleen volume reduction ≥ 35%



Symptom burden reduction ≥ 50%

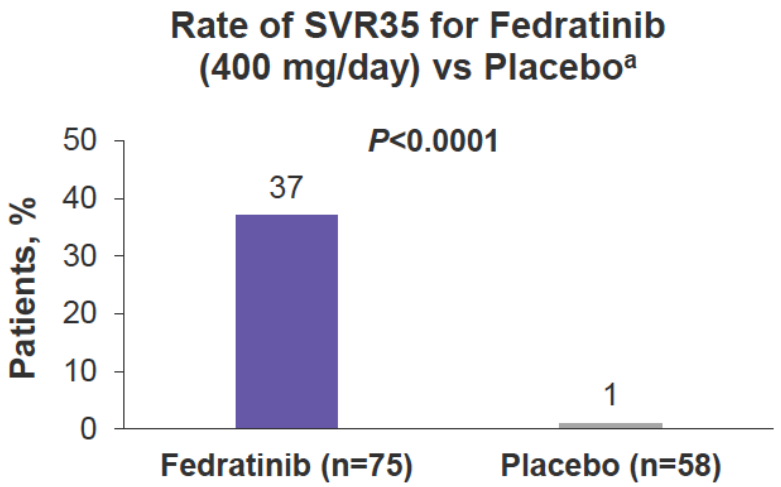
*More stringent criteria for relapse, refractory, and intolerance to ruxolitinib

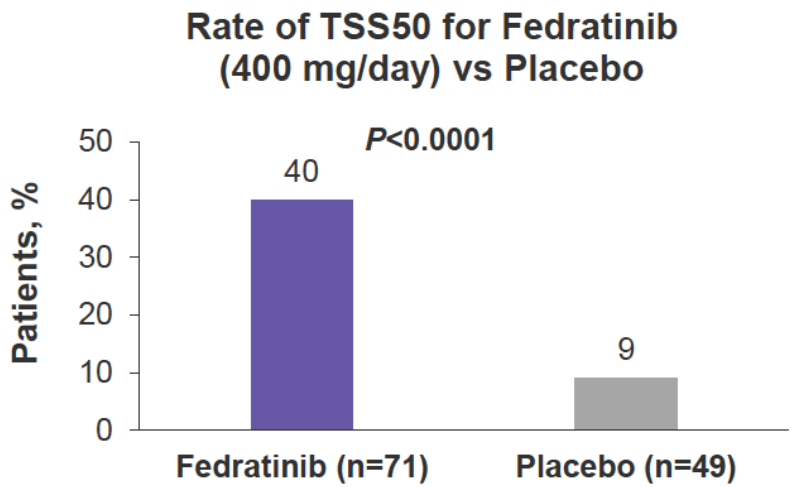
1. Comparable efficacy in low PLT count (50-100)
2. Short-term data may reveal lower risk of infections and second cancers (NMSC) compared to RUX
3. GI toxicity and thiamine depletion require active management
4. No survival data

- AE, adverse event; FED, fedratinib; GI, gastrointestinal; Int-2, intermediate-risk level 2; JAKARTA, Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib; MF, myelofibrosis; NMSC, non-melanoma skin cancers; PLT, platelet; RUX, ruxolitinib.
- [1] Pardanani A, et al. *JAMA Oncol.* 2015;1(5):643-651. [2] ClinicalTrials.gov Phase III Study of SAR302503 in Intermediate-2 and High Risk Patients With Myelofibrosis Available at: https://clinicaltrials.gov/ct2/show/NCT01437787. Accessed June 2, 2023. [3] Harrison CN, et al. Lancet Haematol. 2017;4(7):317-324. [4] Harrison CN, et al. ASCO 2019. Abstract 7057. [5] ClinicalTrials.gov Phase II, Open Label, Single Arm Study of SAR302503 In Myelofibrosis Patients Previously Treated With Ruxolitinib (JAKARTA2) Available at: https://clinicaltrials.gov/ct2/show/NCT01523171. Accessed June 2, 2023.

JAKARTA trial in ND MF: risposte spleniche e sintomi

Change in Spleen Volume and Symptoms at 24 Weeks[1]





- Fedratinib therapy significantly **reduced splenomegaly** and **symptom burden** compared with placebo in patients with MF[1]
- **TSS response rate** was significantly **higher with fedratinib** vs placebo (**36% or 34%** for the 400-mg and 500-mg fedratinib doses, respectively, vs **7%**; *P*<0.001)[2]; clinically meaningful improvements from baseline in individual symptoms and on the EQ-5D were also subsequently reported[3]

Pardanani A, et al. *JAMA Oncol.* 2015;1(5):643-651.

Qual’è la tossicità di fedratinib

- The **rate of discontinuation** of the study drug due to **AEs** was **14%** in the **fedratinib** arm and **8%** in the **placebo** arm[1]
- **Common AEs** (≥20%) with **fedratinib** were **anaemia**, diarrhoea, nausea, and vomiting[1]
- **Anaemia** was the most common **grade ≥3** event (30%), and no other grade ≥3 AEs occurred in >5% of patients[1]
- In patients receiving fedratinib, AEs resulted in:[1]
  - **Dose reductions** in **19%** of patients
  - **Dose interruptions** in **21%** of patients
- A clinical development hold resulted in a boxed warning for **encephalopathy**, including **Wernicke encephalopathy**[2]
  - **Thiamine levels** must be assessed in all patients before starting treatment and periodically during treatment[2]

AEs, %[1]	Fedratinib 400 mg (n=96)		Placebo (n=95)[a]	
	All grades	Grade ≥3[b]	All grades	Grade ≥3
Diarrhoea	66	5	16	0
Nausea	62	0	15	0
Anaemia	40	30	14	7
Vomiting	39	3	5	0
Fatigue or asthenia	19	5	16	1
Muscle spasms	12	0	1	0
Blood creatinine increased	10	1	1	0
Pain in extremity	10	0	4	0
ALT increased	9	0	1	0
Headache	9	0	1	0
Weight increased	9	0	4	0
Dizziness	8	0	3	0
Bone pain	8	0	2	0
Urinary tract infection (including cystitis)	6	0	1	0
Dysuria	6	0	0	0
AST increased	5	0	1	0

Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651.

Fedratinib: FREEDOM study design

Screening

Key inclusion criteria

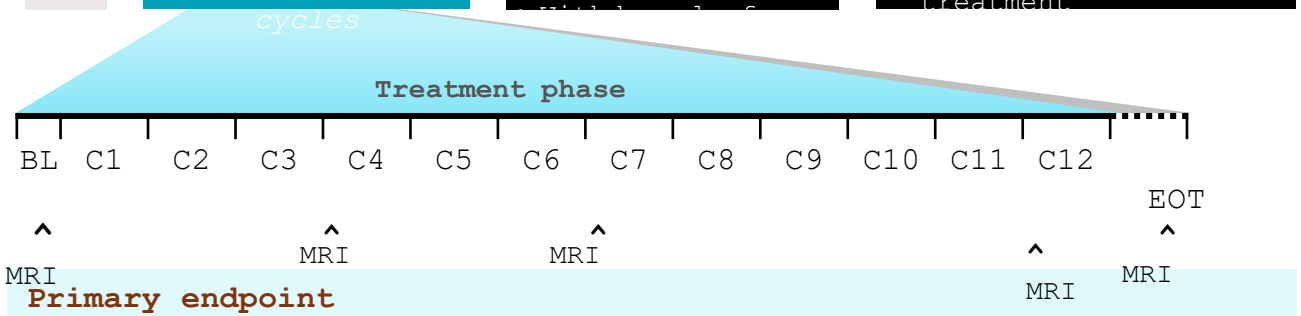
- Age ≥ 18 years
- WHO[2]-defined primary, post-PV, or post-ET MF
- DIPSS[3] intermediate-1, intermediate-2, or high-risk MF
- ECOG PS score 0–2
- Splenomegaly ≥ 450 cm^3 (MRI) or palpable spleen ≥ 5 cm below LCM
- Prior ruxolitinib treatment for ≥ 3 months, or for ≥ 28 days with development of RBC TD (≥ 2 units/month for 2 months) or grade ≥ 3 thrombocytopenia, anemia, hematoma, or hemorrhage
- Platelet count ≥ 50 × 10^9/L
- ANC ≥ 1.0 × 10^9/L
- Peripheral blasts < 5%
- Normal thiamine level

Enrollment N ≈ 110

Treatment phase
Fedratinib 400 mg QD
Continuous 28-day treatment cycles

Treat until
- Lack of efficacy
- Intolerance
- Disease progression

EOT/follow-up
- Patients followed for AEs (30 days) and survival (12 months) after treatment



Primary endpoint
- Spleen RR: proportion of patients with ≥ 35% SVR from BL at EOC6

Key secondary endpoints
- Safety
- Duration of spleen response
- Spleen size reduction
- Symptom RR and duration
- Risk-mitigation strategies for GI AEs, neurotoxicity, and WE

Exploratory endpoints
- Survival
- Patient-reported outcomes
- Biomarkers of fedratinib efficacy and biochemical activity

- 38 pazienti sono stati arruolati e trattati (arruolamento interrotto in anticipo per Covid-19)
- Al termine del database (novembre 2021), la durata mediana del trattamento era di 38 (2-124) settimane
- 13 pazienti avevano FEDR in corso; 25 pazienti avevano interrotto FEDR

Strategie di mitigazione degli eventi avversi:
- Uso profilattico/sintomatico di Tx antiemetico/vomitico e antidiarroico
- Somministrazione di fedratinib con il cibo
- Modifiche al dosaggio di Fedratinib
- Integrazione di tiamina

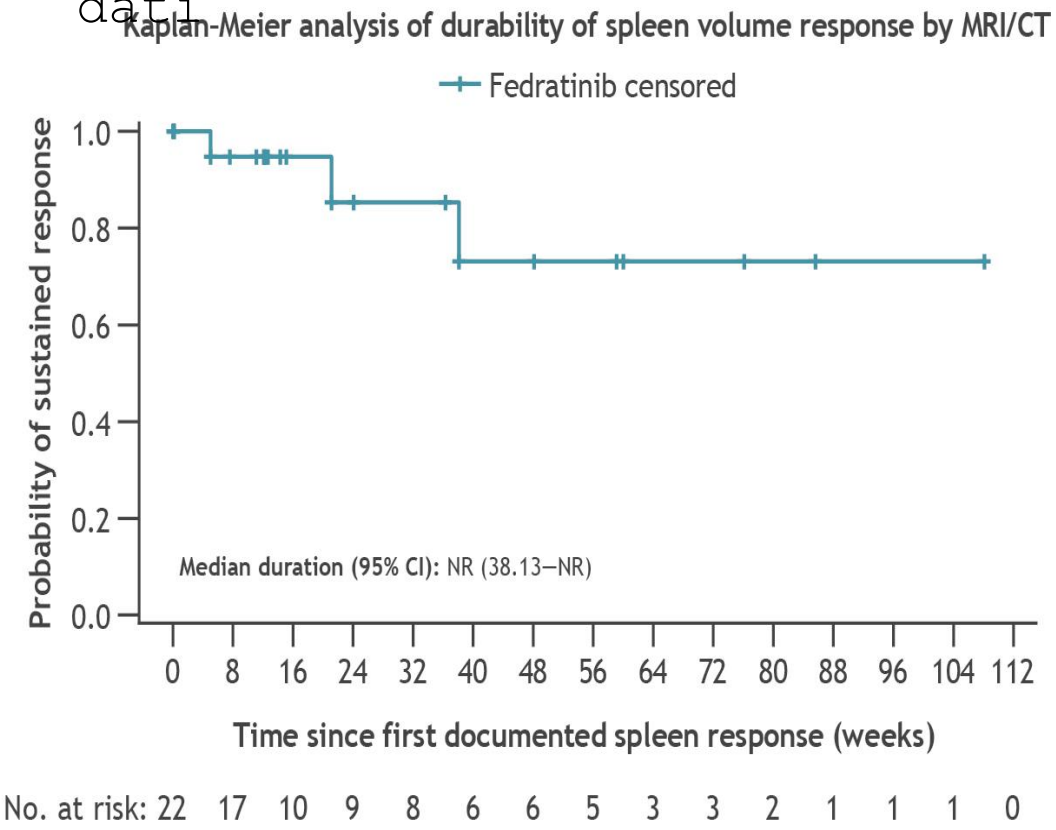
Gupta et al, ASH 2022, abs 1711

FEDR efficacia sul volume della milza e sui sintomi (N=38)

Response parameter	N*
SVR35 at EOC6 (n = 35)	9 (25.7)
Sensitivity analysis of SVRR (n = 35)	
≥ 35% SVR EOC6 (with LOCF)	13 (37.1)
Best overall response	22 (62.9)
≥ 25% SVR EOC6 (with LOCF)	24 (68.6)
Best overall response	30 (85.7)

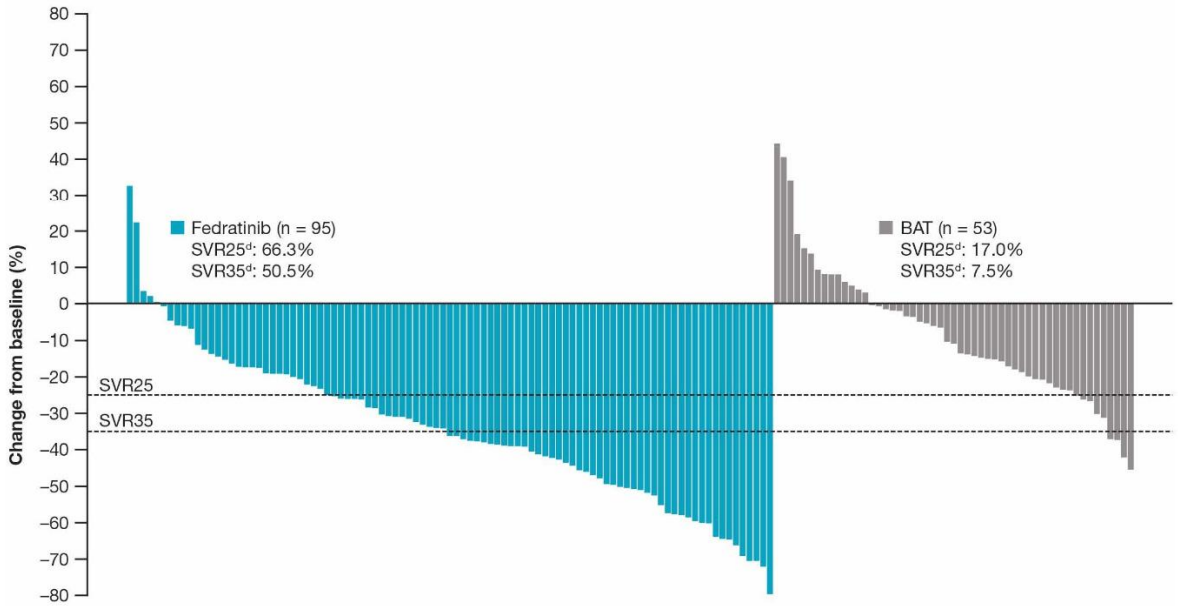
*LOCF: last observation carried forward; * % of evaluable*

- Dei rispondenti SVR35, 19/22 (86,4%) hanno mantenuto una risposta duratura al cutoff dei dati



Gupta et al, ASH 2022, abs 1711

FREEDOM2: tossicità ed efficacia



- 201 pts randomized to fedra (134) and BAT (67)
- 46 treated with BAT crossover to fedra
- Median age 70 years, 54.7% primary MF

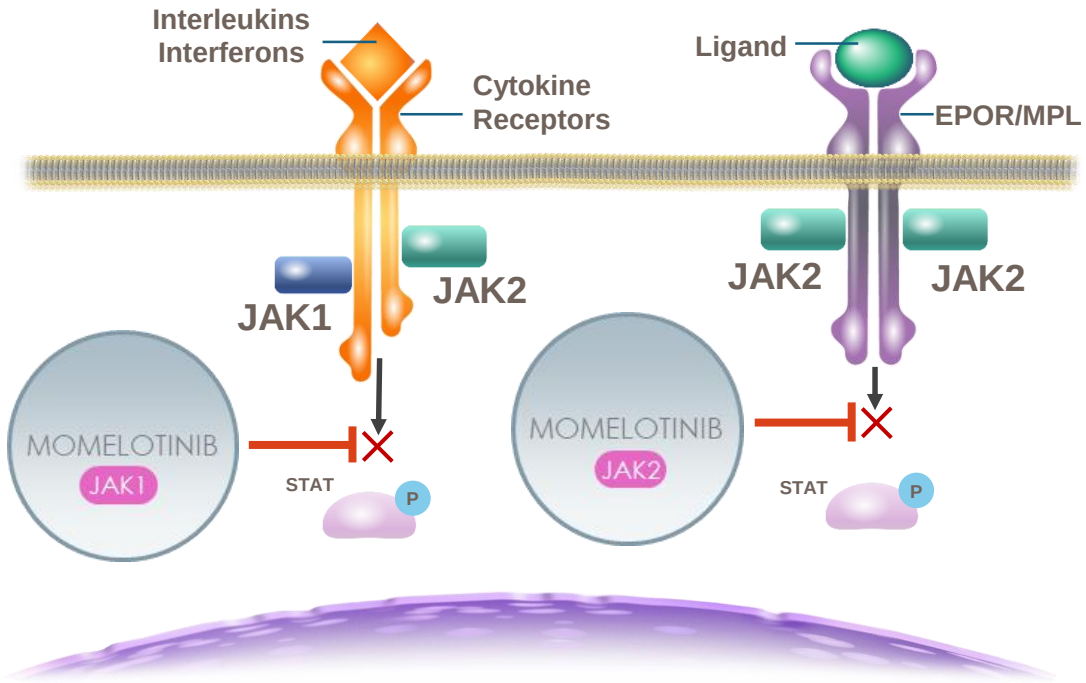
- SVR35% at EOC6 35.8% vs 6%
- TSS50% 34% vs 16.9%

- Dose interruption/reduction 52% vs 30%
- Most frequent AEs with fedra were diarrhoea (38%), nausea (32%)
- 16% patients had thiamine lower than normal

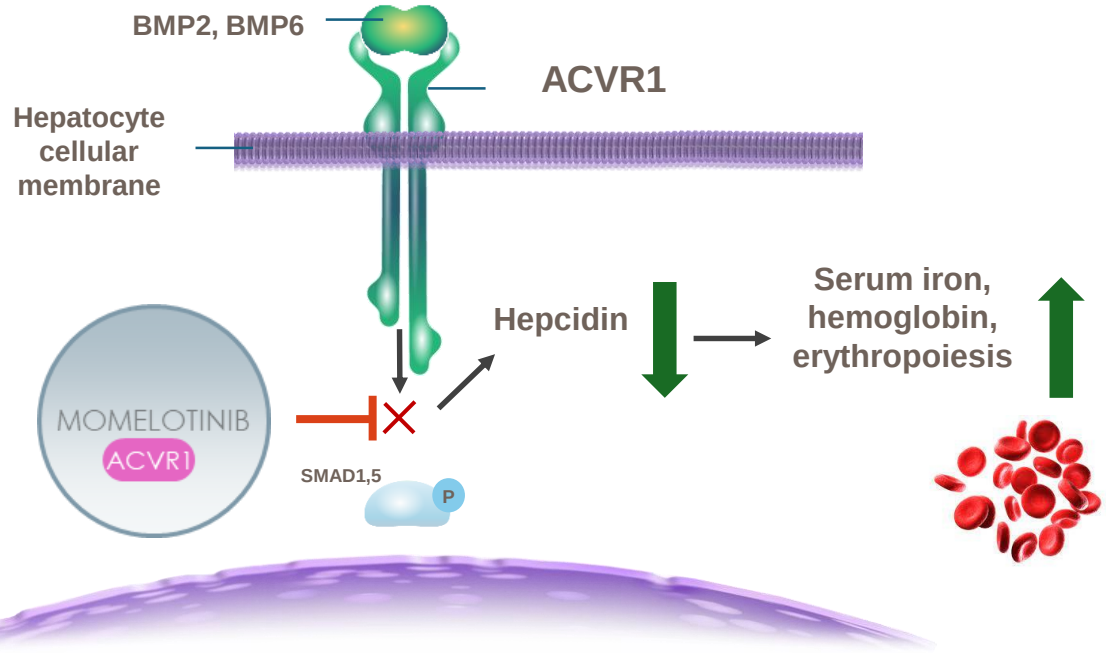
- 1 case of Wernicke's enecephaolopathy suspected at cycle 3 with fedra

Harrison et al, ASH 2023, abs 3204

Momelotinib è un inibitore di JAK1, JAK2, e ACVR1



Dysregulated **JAK-STAT signaling** in MF drives overproduction of inflammatory cytokines, **bone marrow fibrosis, systemic symptoms,** and clonal proliferation resulting in extramedullary hematopoiesis and **splenomegaly**[1,2]



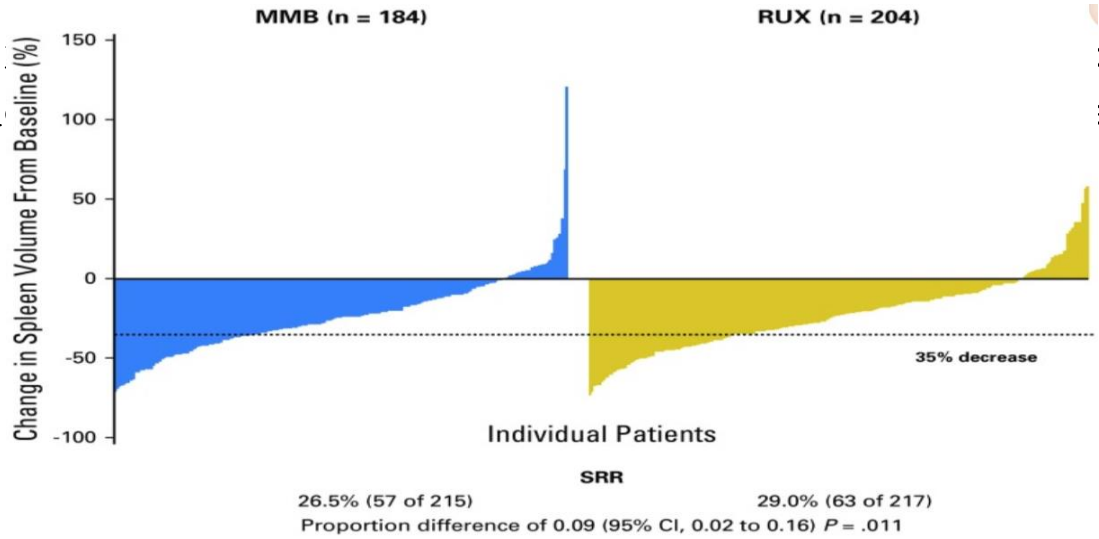
Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF[3,4]

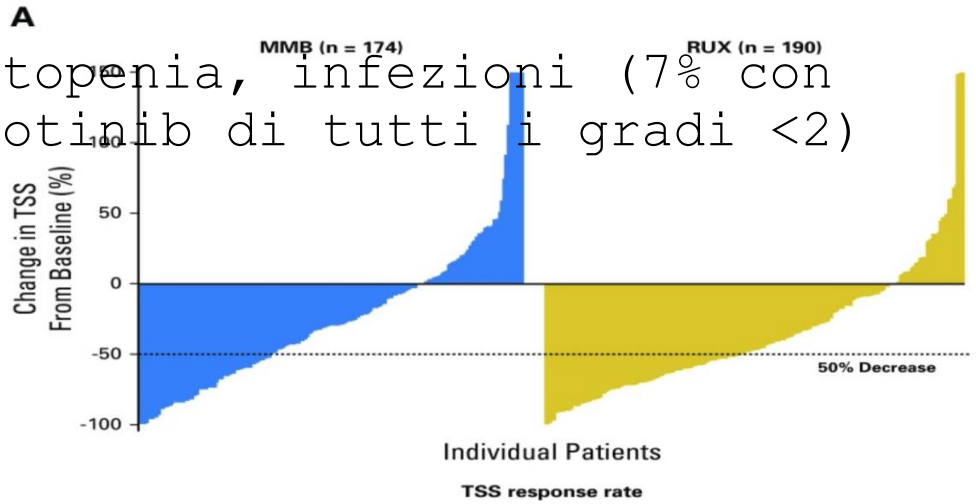
ACVR1, activin A receptor type 1; BMP, bone morphogenetic protein; EPOR, erythropoietin receptor; JAK, Janus kinase; MF, myelofibrosis; MPL, myeloproliferative leukemia protein; SMAD1/5, mothers against decapentaplegic homolog 1/5; STAT, signal transducer and activator of transcription.

1. Chifotides HT, et al. *J Hematol Oncol*. 2022;15(1):7. 2. Verstovsek S, et al. *Future Oncol*. 2021;17(12):1449-1458. 3. Asshoff M, et al. *Blood*. 2017;129(13):1823-1830. 4. Oh ST, et al. *Blood Adv*. 2020;4(18):4282-4291.

Momelotinib in MF: Simplify-1 trial

- 432 pazienti con MF interm2/ad alto rischio o sintomatica int1 sono stati arruolati e randomizzati a momelotinib 200 mg o ruxo 20 mg BID per 24 settimane
- Endpoint primario: risposta della milza (riduzione >35% del volume della milza rispetto al basale)
- **Endpoint raggiunto dal 26,5% dei pazienti con momelotinib 200 mg e dal 29% nel braccio ruxo**
- Una riduzione >50% della TTS è stata osservata rispettivamente nel 28,4% vs 42% nei bracci momelotinib e ruxo. L'indipendenza trasfusionale è stata migliorata con momelotinib
- Eve citopenia, infezioni (7% con mom elotinib di tutti i gradi <2)

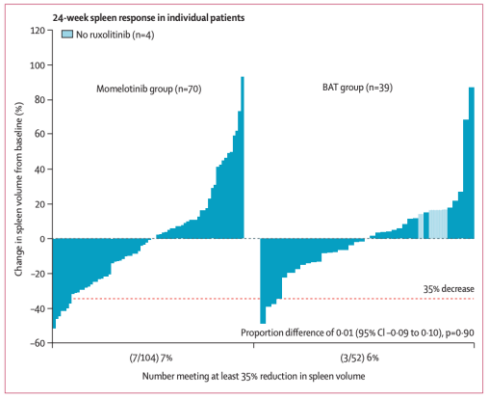


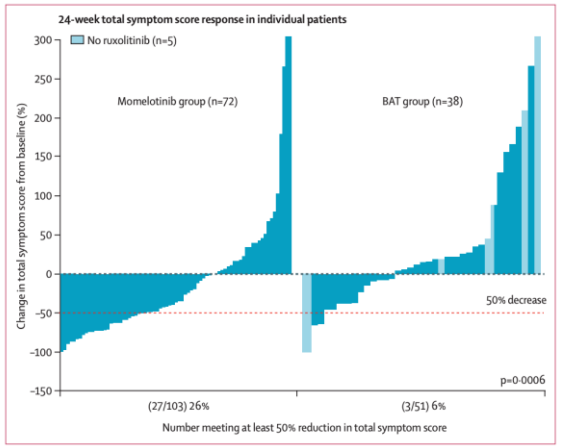


Mesa et al J Clin Oncol 2017; 35: 3844-3850

Momelotinib in MF: Simplify-2 trial

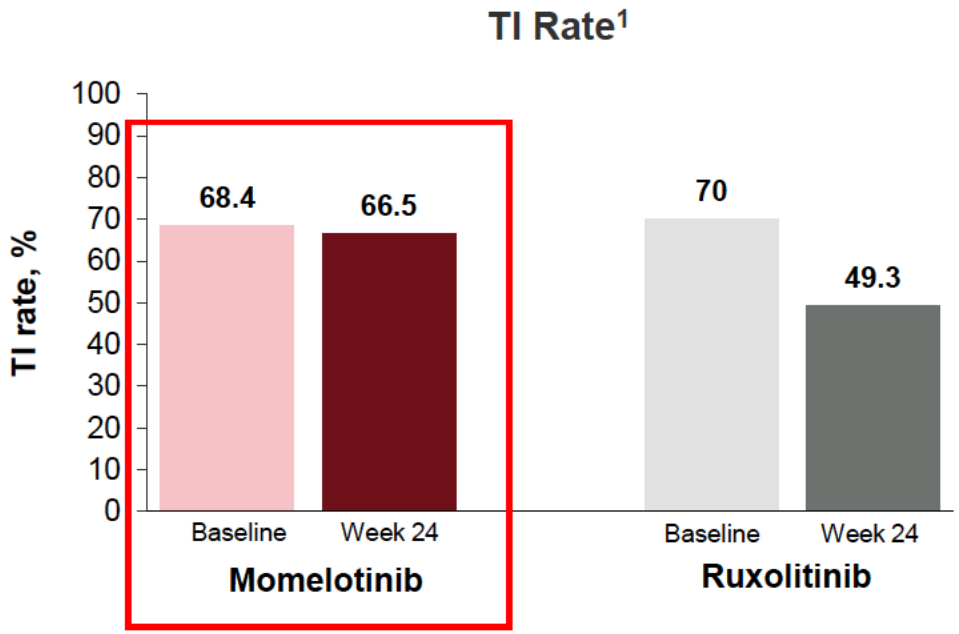
- Studio di fase 3 vs BAT: pazienti con MF e precedente trattamento con ruxolitinib per almeno 28 giorni che hanno richiesto trasfusioni di globuli rossi durante il trattamento con ruxolitinib o riduzione della dose di ruxolitinib a meno di 20 mg due volte al giorno con almeno una trombocitopenia di grado 3, nello studio sono stati inclusi anemia o sanguinamento di grado 3 o peggiore, con milza palpabile di almeno 5 cm e senza neuropatia periferica di grado 2 o superiore.
- 156 pazienti arruolati (2:1): 73 (70%) dei 104 pazienti nel gruppo momelotinib e 40 (77%) dei 52 pazienti nel gruppo BAT hanno completato la fase di trattamento di 24 settimane.
- Il **7% dei pazienti nel gruppo momelotinib e il 6% nel gruppo BAT hanno avuto una riduzione del volume della milza di almeno il 35% rispetto al basale**
- Gli eventi avversi g sono stati anemia (14 [14%] su 104 nel g i u 52 nel gruppo BAT), trombocitopenia (s e ddominale (uno [1%] contro tre [6%]). e ficata in 11 (11%) dei 104 pazienti tratt i





Harrison et al Lamcet Hematol 2018; 5: 73-81

Simplify-1 trial: si mantiene la trasfusione-indipendenza



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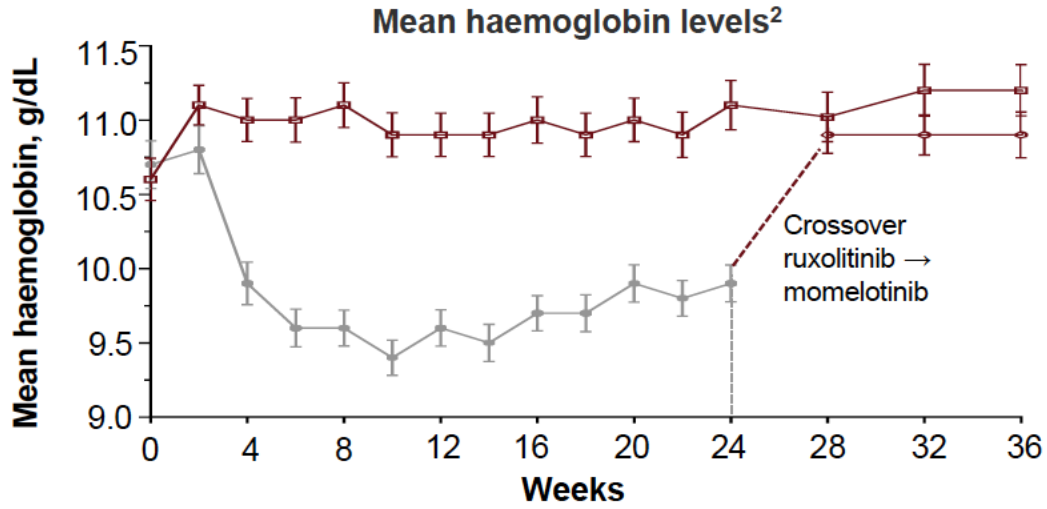
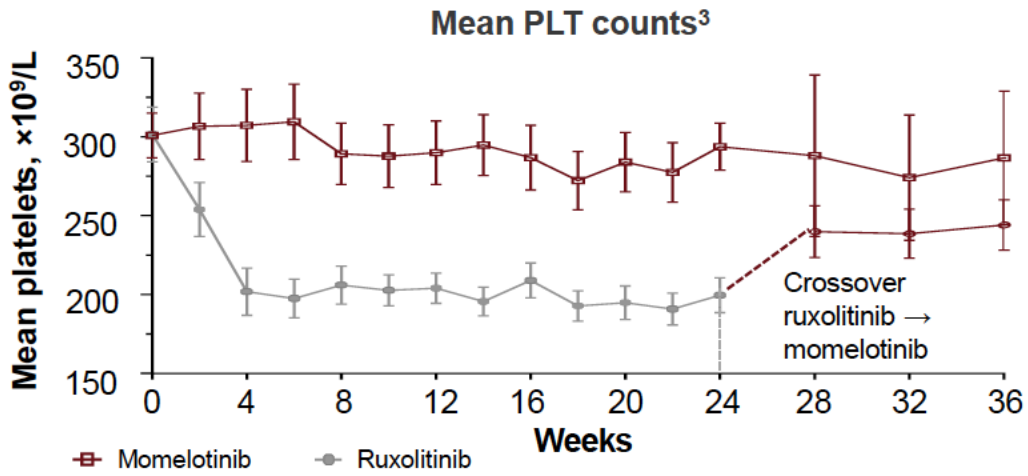


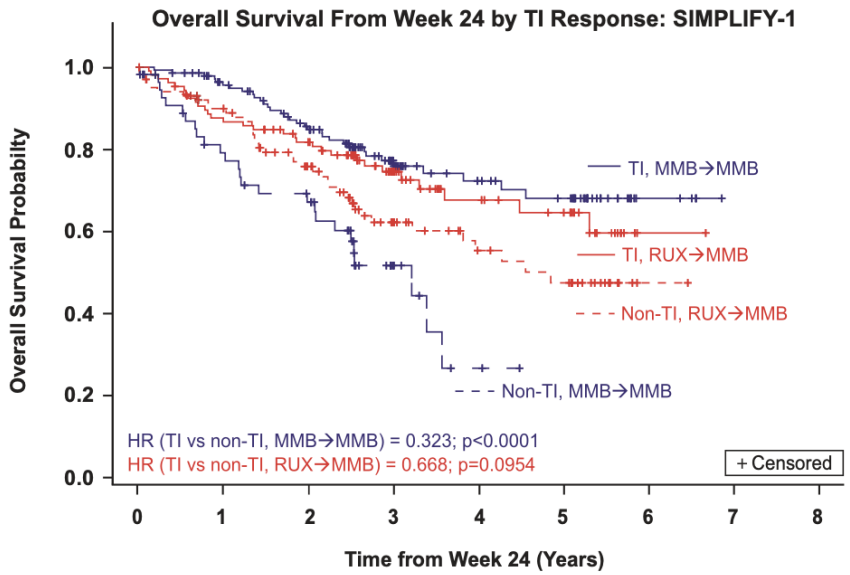
Harrison C, et al. Presented at the European Hematology Association 25th Annual Congress 2020. Poster EP1113. Reprinted with permission by the author.



Mesa et al J Clin Oncol 2017; 35: 3844-3850

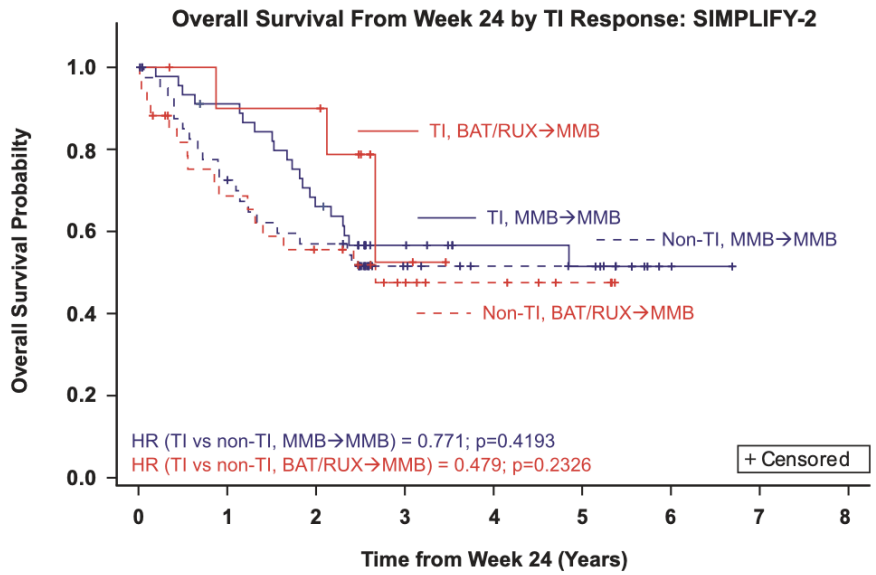
Chi ottiene la trsfusione indipendenza ha un vantaggio di sopravvivenza

A



TI, MMB→MMB	142	127	105	57	37	31	5	0
TI, RUX→MMB	107	90	79	43	25	20	1	0
Non-TI, MMB→MMB	56	40	32	9	2	0		
Non-TI, RUX→MMB	102	86	63	34	22	18	1	0

B



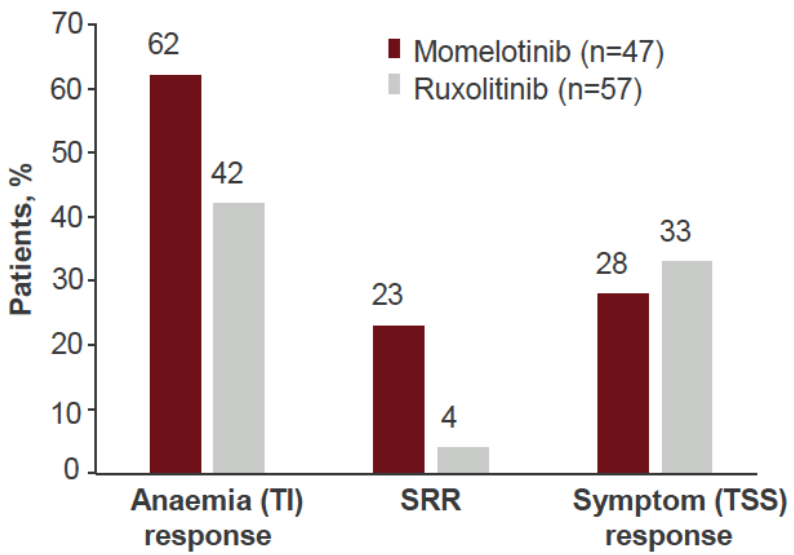
TI, MMB→MMB	45	40	29	16	11	10	2	0
TI, BAT/RUX→MMB	11	9	9	2	0			
Non-TI, MMB→MMB	43	29	22	7	3	2	0	
Non-TI, BAT/RUX→MMB	34	21	16	9	6	3	0	

- In SIMPLIFY-1, patients randomized to momelotinib who were TI-Rs at week 24 had an OS advantage (3-y OS in momelotinib TI-Rs was 80% compared with 50% in momelotinib TI-NRs, HR=0.30; *P*<0.0001).
- A trend toward improved OS in TI responders was also observed in the JAKi-exposed SIMPLIFY-2 population.

Efficacia anche nei pazienti con piastrinopenia

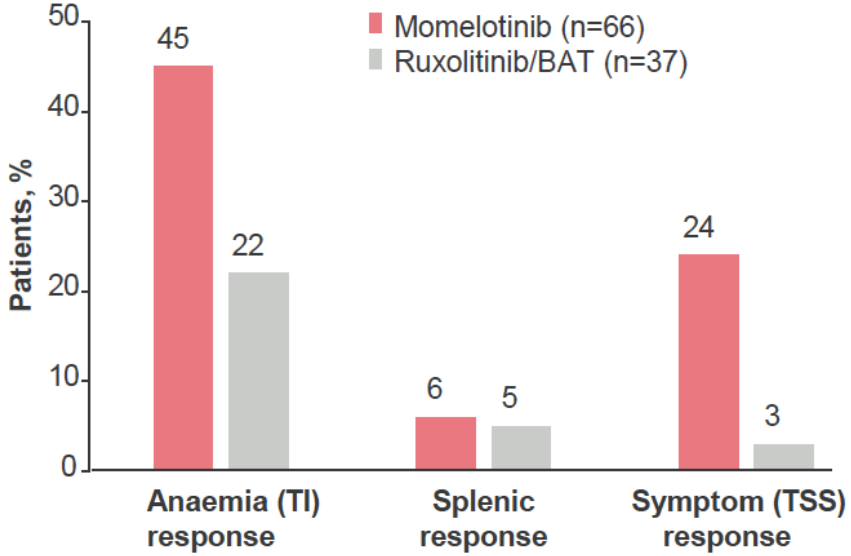
SIMPLIFY-1[1]

Patients with PLT 50-150×10⁹/L at baseline[a]



SIMPLIFY-2[1]

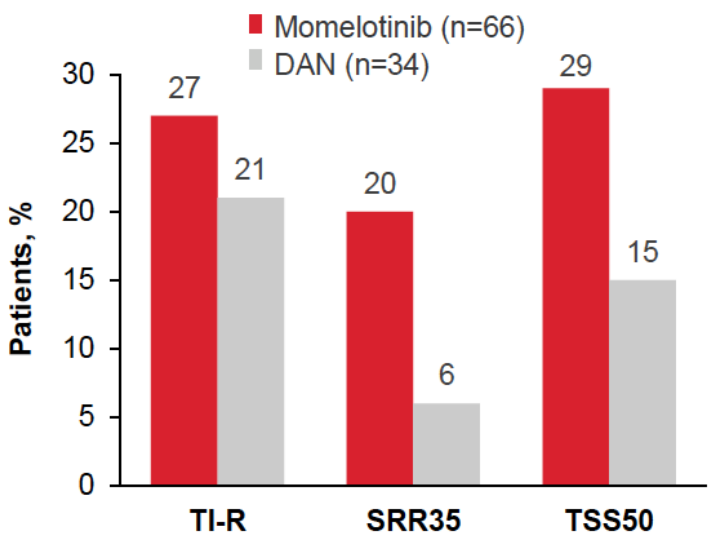
Patients with PLT ≤150×10⁹/L at baseline



Kiladjian JJ, et al. Presented at the 2020 American Society of Hematology Annual Meeting. Abstract 3086. Reprinted with permission by the author.

MOMENTUM[2]

Patients with PLT ≤100×10⁹/L at baseline



Gerds AT, et al. Presented at the 64th American Society of Hematology Annual Meeting & Exposition 2022. Oral presentation 627. Reprinted with permission by the author.

Mesa et al J Clin Oncol 2017; 35: 3844-3850

Tossicità di momelotinib

- In pooled safety analysis, the most common non-haematological AEs (≥15%) were **diarrhoea** (26.8%), **nausea** (19.4%), **fatigue** (17.5%), **cough** (17.4%), and **dizziness** (15.4%)[1]
  - **Pneumonia** was the most common grade ≥3 AE in 8.4%
- **Fatal AEs** were reported in 102 (14.1%) patients, with **pneumonia** being the most common (n=9), followed by **acute myeloid leukemia** (n=6) and **sepsis** (n=5)[1]
  - All were reported as **unrelated** to study drug[2]
- The total follow-up time was 1261 person-years as of data cutoff[a]; **12.1%** of patients were treated for **≥5 years** with momelotinib[1]

	Momelotinib overall (N=725)[1,a]	
n (%)	**Any-grade TEAE**	**Grade ≥3 TEAE**
Nonhaematologic AEs		
Diarrhoea	194 (26.8)	19 (2.6)
Nausea	141 (19.4)	8 (1.1)
Fatigue	127 (17.5)	18 (2.5)
Cough	126 (17.4)	5 (0.7)
Dizziness	112 (15.4)	4 (0.6)
Abdominal pain	102 (14.1)	13 (1.8)
Pyrexia	102 (14.1)	9 (1.2)
Headache	101 (13.9)	6 (0.8)
Asthenia	96 (13.2)	8 (1.1)
Pruritus	90 (12.4)	5 (0.7)
Dyspnoea	89 (12.3)	15 (2.1)
Peripheral sensory neuropathy	89 (12.3)	5 (0.7)
Urinary tract infection	88 (12.1)	18 (2.5)
Pneumonia	83 (11.4)	61 (8.4)
Constipation	81 (11.2)	1 (0.1)
Peripheral oedema	75 (10.3)	5 (0.7)
Arthralgia	73 (10.1)	2 (0.3)
Upper respiratory tract infection	73 (10.1)	3 (0.4)
Select haematologic AEs		
Thrombocytopenia	181 (25.0)	119 (16.4)
Anaemia	170 (23.4)	107 (14.8)
Neutropenia	49 (6.8)	35 (5.2)

Verstovsek S, et al. Blood Adv. 2023. Online ahead of print.
Verstovsek S, et al. ASH 2022. Poster 4348.

Pacritinib is a potent ACVR1 inhibitor

- **Pacritinib is ~4x more potent** than momelotinib against ACVR1

	+ Control LDN 193189[a]	PAC C_{max} 213 nM	MMB C_{max} 168 nM	FED C_{max} 275 nM	RUX C_{max} 47 nM
Replicate 1 ACVR1 IC_{50} (nM)	20.4	22.6	70.2	312.0	>1000
Replicate 2 ACVR1 IC_{50} (nM)	32.4	10.8	34.9	235.0	>1000
Mean ACVR1 IC_{50} (nM)	26.4	16.7	52.6	273.5	>1000
Potency[b] (C_{max}:IC_{50})	N/A	12.7	3.2	1.0	<0.01

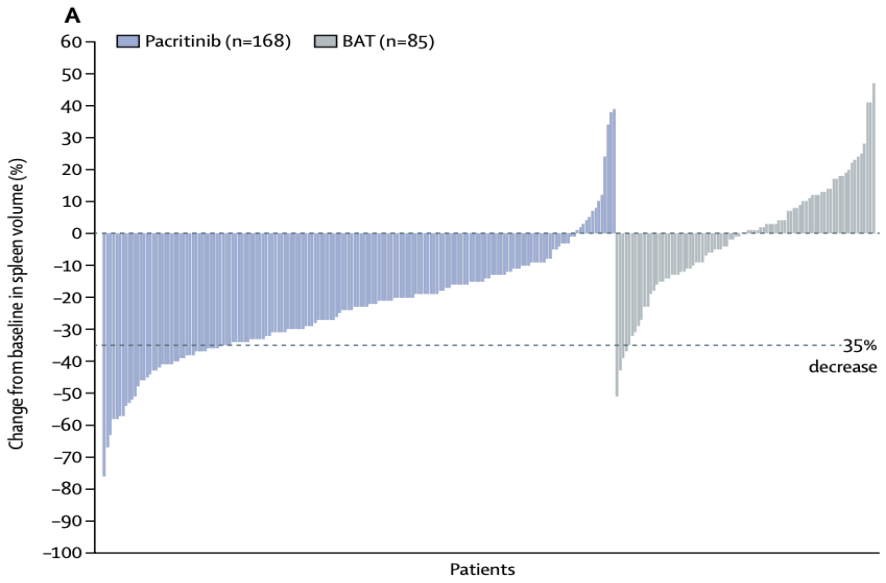
Legend: Higher potency → Lower potency

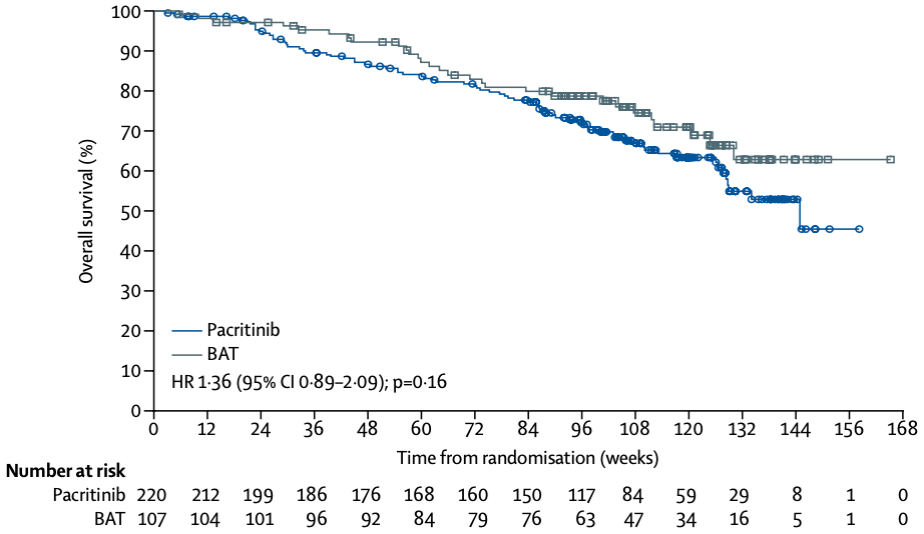
[a]LDN 193189 is an ACVR1 inhibitor.
[b]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.

Oh et al ASH 2022

Pacritinib in MF: Persist-1 trial

- Fase 3 randomizzato vs BAT (escluso ruxo)
- 327 pazienti arruolati e randomizzati a pacritinb 400 mg QD o BAT (2:1)
- L'endpoint primario era la riduzione del volume della milza > 35% alla settimana 24
- **Riduzione del volume della milza 19% pacritinib vs 5% braccio BAT**
- Gli effetti indesiderati più comuni sono stati anemia, trombocitopenia, diarrea, aumento del rischio di insufficienza cardiaca (5%)

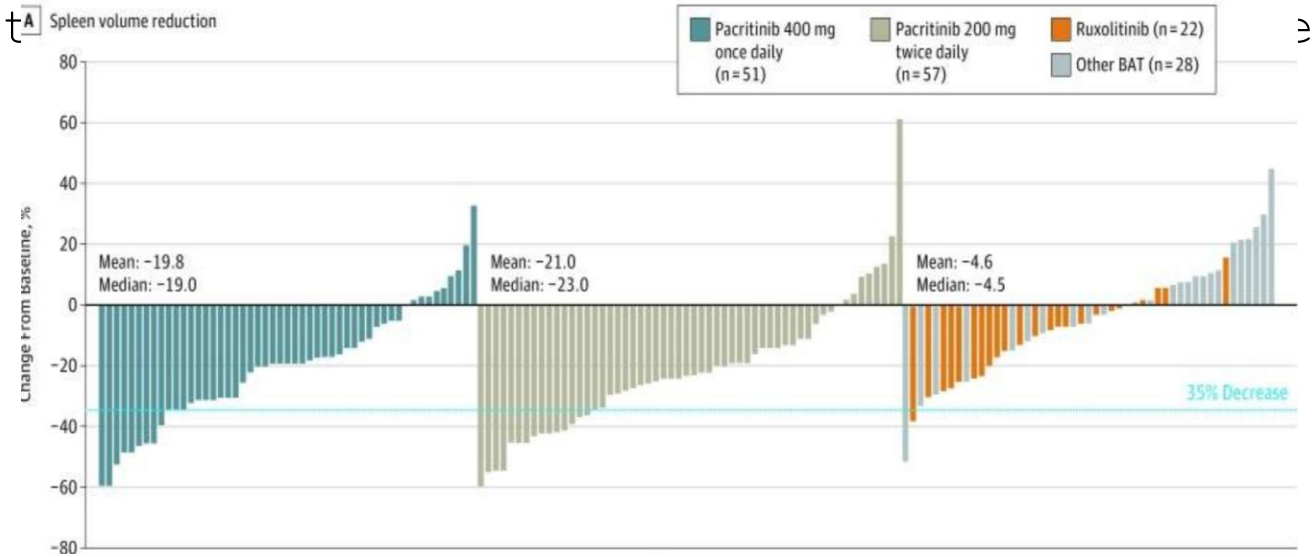




Mesa et al Lancet Hematol 2017; 4: 225-236

Pacritinib in MF: Persist-2 trial

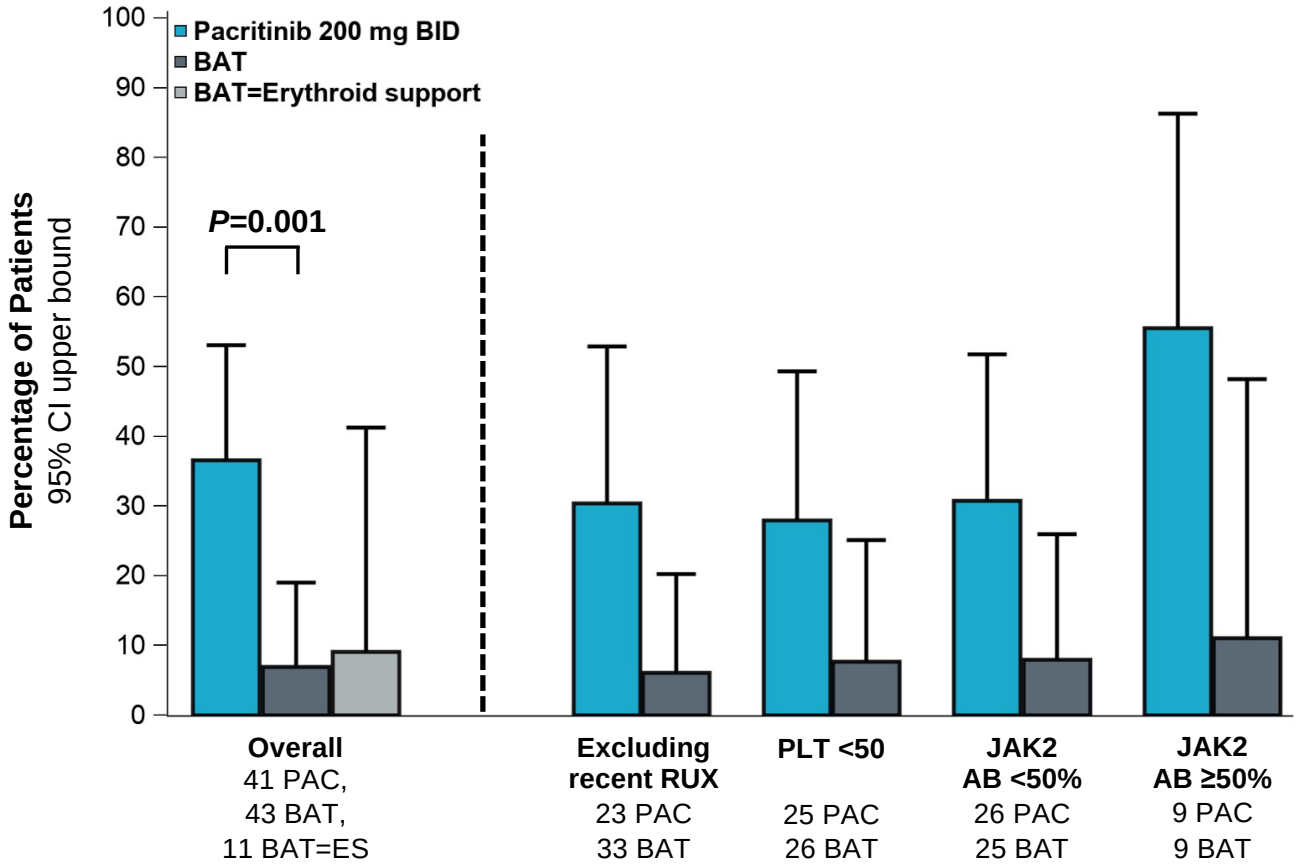
- Fase 3 randomizzato vs BAT
- 311 pazienti arruolati e randomizzati a pacritinb 400 mg QD, 200 mg BID o BAT (48% precedentemente trattati con ruxo) con conta plt ≤ 100 x 109/L
- Gli endpoint co-primari erano la riduzione del volume della milza > 35% e una riduzione del 50% o più del TSS alla settimana 24
- **Riduzione del volume della milza 18% pacritinib vs 3% braccio BAT; TSS 25% contro 14%. Più risposte nel braccio pacritinib BID (anche per dipendenza da trasfusioni)**
- Gli effetti collaterali più comuni sono stati eventi avversi gastrointest[illegible] vertigini



Mascarenhas et al JAMA 2018; 4: 652-659

Trasfusione Indipendenza con pacritinib nel PERSIST-2

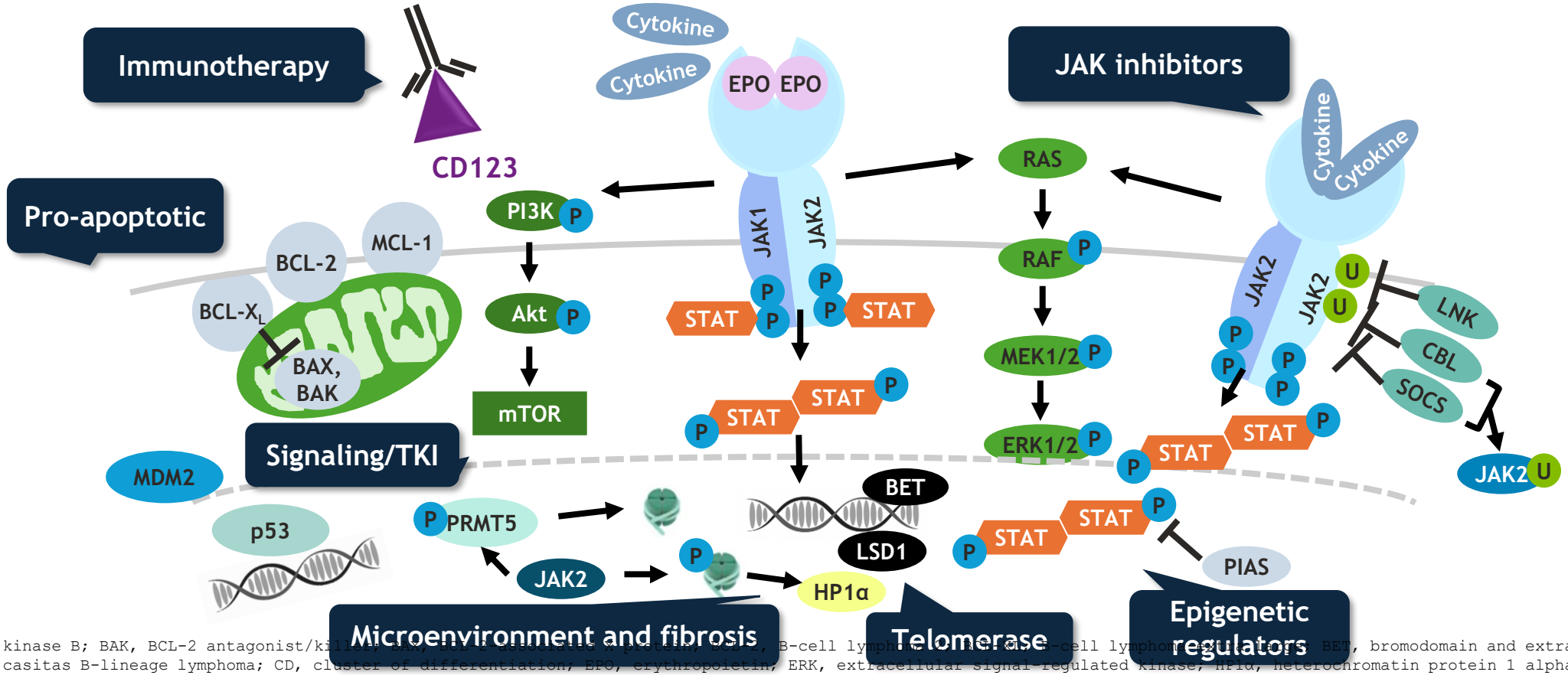
PERSIST-2 (PAC vs. BAT in JAKi exposed, PLT<100x10⁹/L): conversion rate (no RBC transfusion over 12W)



Pacritinib N=41	BAT N=43	*P*-value
37%	7%	0.001

Oh et al. ASH 2022. abs

Il futuro con associazioni di farmaci nuovi



Akt, protein kinase B; BAK, BCL-2 antagonist/killer; BAX, BCL-2 associated X protein; BCL, B-cell lymphoma; BCL-XL, B-cell lymphoma-extra large; BET, bromodomain and extra-terminal domain; CBL, casitas B-lineage lymphoma; CD, cluster of differentiation; EPO, erythropoietin; ERK, extracellular signal-regulated kinase; HP1α, heterochromatin protein 1 alpha; JAK, Janus kinase; LNK, lymphocyte adapter protein; LSD, lysine-specific histone demethylase; MCL-1, myeloid cell leukemia-1; MDM2, murine double minute 2; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; P, phosphorylation; PI3K, phosphatidylinositol-3 kinase; PIAS, protein inhibitors of activated STATs; PRMT5, protein arginine methyltransferase 5; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TKI, tyrosine kinase inhibitor; U, ubiquitination.

1. Daver N & Assi R. Oncol Hematol Rev. 2016;**12**:71–74; 2. McLornan DP & Harrison CN. Br J Haematol. 2020;191:21–36; 3. Pettit K, et al. ASCO Educ Book. 2022;42:595–613; 4. Tremblay D & Mascarenhas J. Cells. 2021;10:1034; 5. Petiti J, et al. J Cell Mol Med. 2020;24:10978–10986; 6. Guo J, et al. PLoS One. 2015;10:e0114363; 7. McPherson S, et al. J Cell Mol Med. 2017;21:1660–1667; 8. Niu GJ, et al. Front Immunol. 2018;9:2392; 9. Nguyen HM & Gotlib J. Am Soc Clin Oncol Educ Book. 2012;32:411–418.

Grazie per l'attenzione!

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