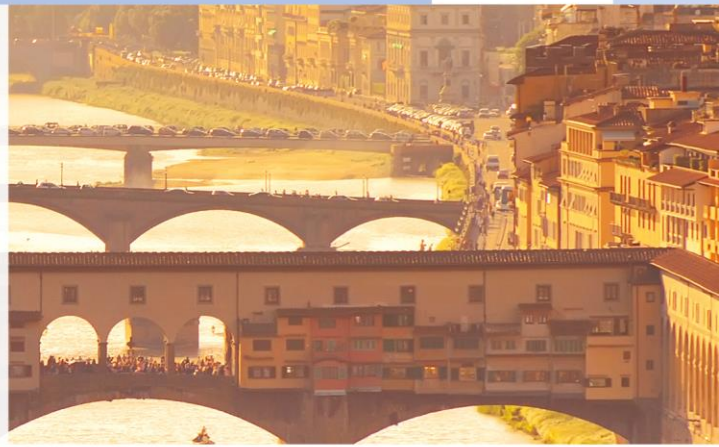
8° WORKSHOP IN EMATOLOGIA TRASLAZIONALE

DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

Firenze - Auditorium CTO - A.O.U. Careggi, 22-23 giugno 2023



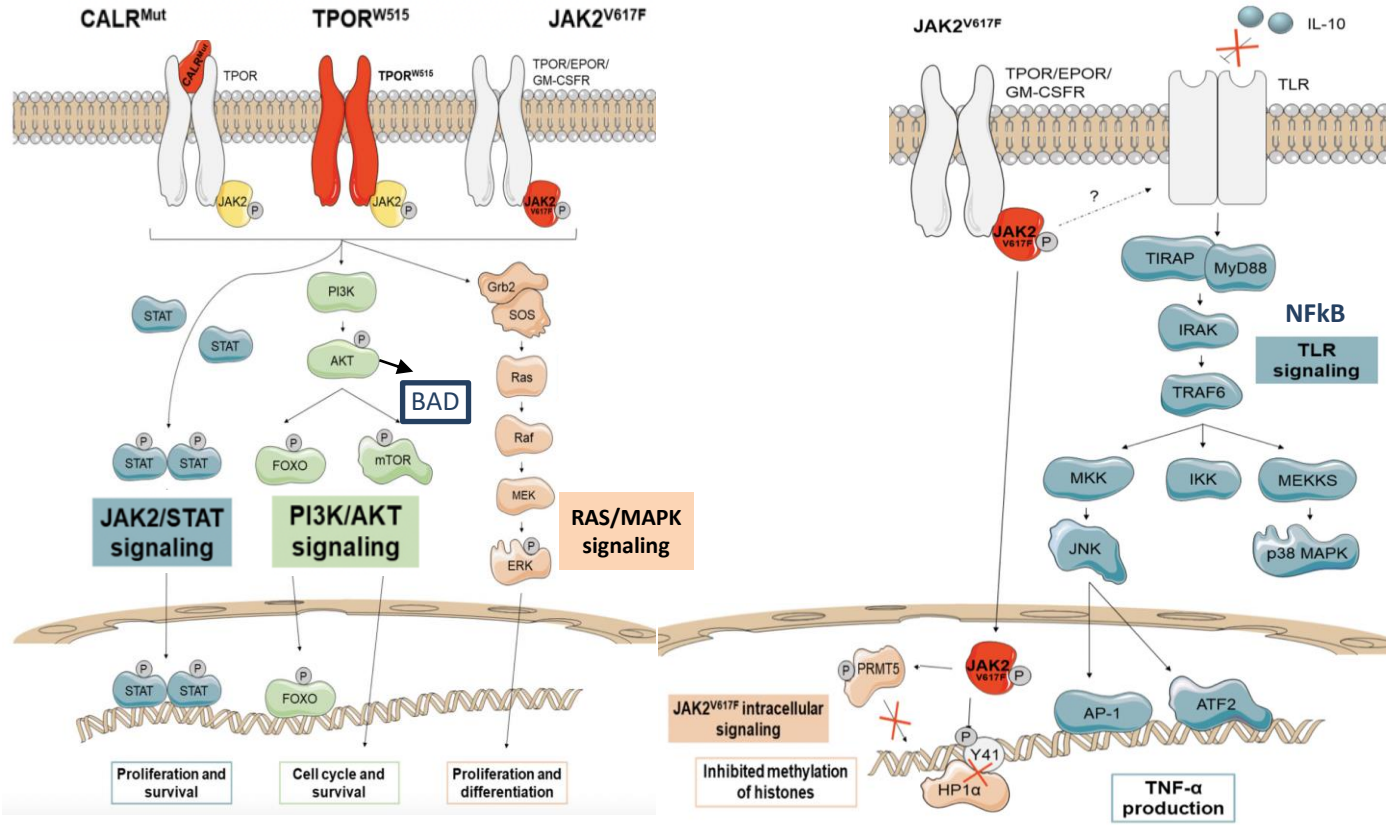
Resistenza primaria e secondaria a JAK inibitori nella mielofibrosi

Barbara Mora, Ematologia, ASST Sette Laghi, Varese

Disclosures of Barbara Mora

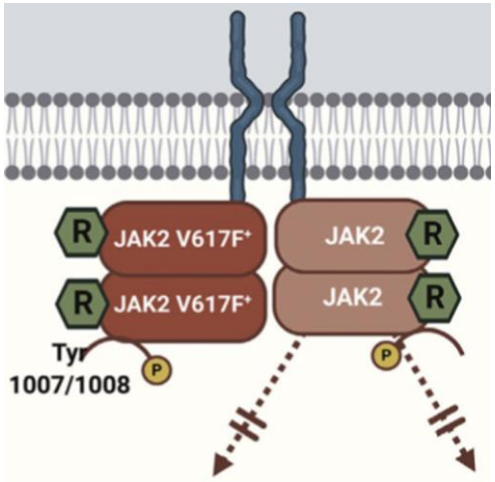
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis					X		

Altered JAK2-related pathways are central for MF pathogenesis

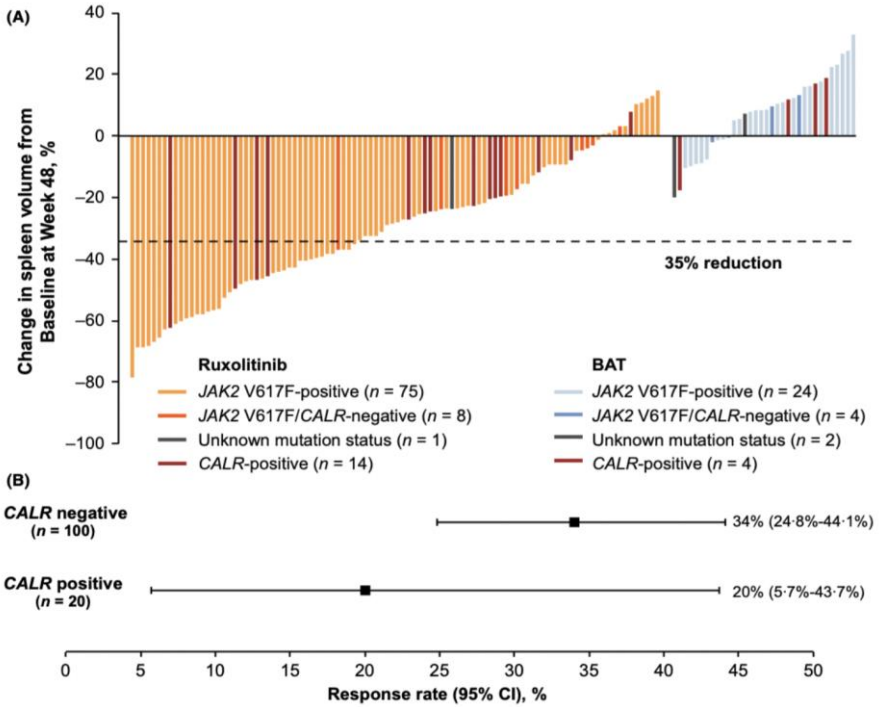


Rampal et al, Blood 2014; Meyer&Levine, Clin Cancer Res 2014; Guijarro-Hernandez&Vizmanos, Cancers 2021

Type 1 JAK inhibitors (JAKi): mechanism of action



R Ruxolitinib (RUX), JAK1/2-i

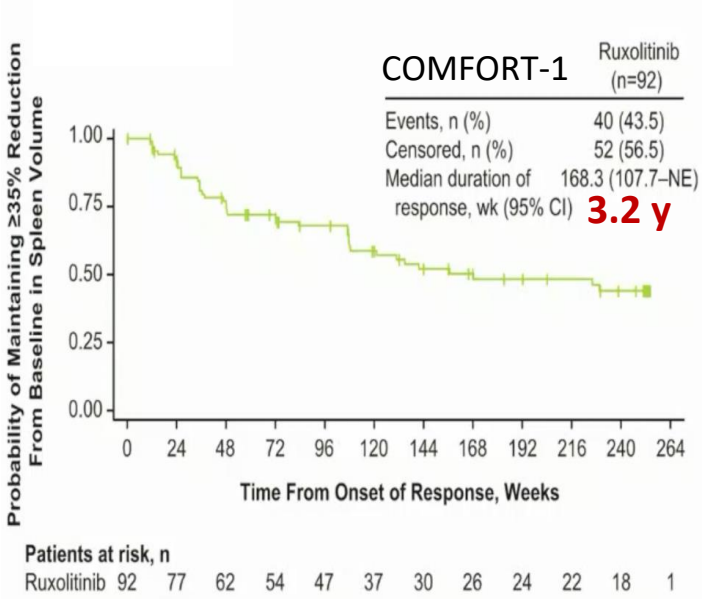


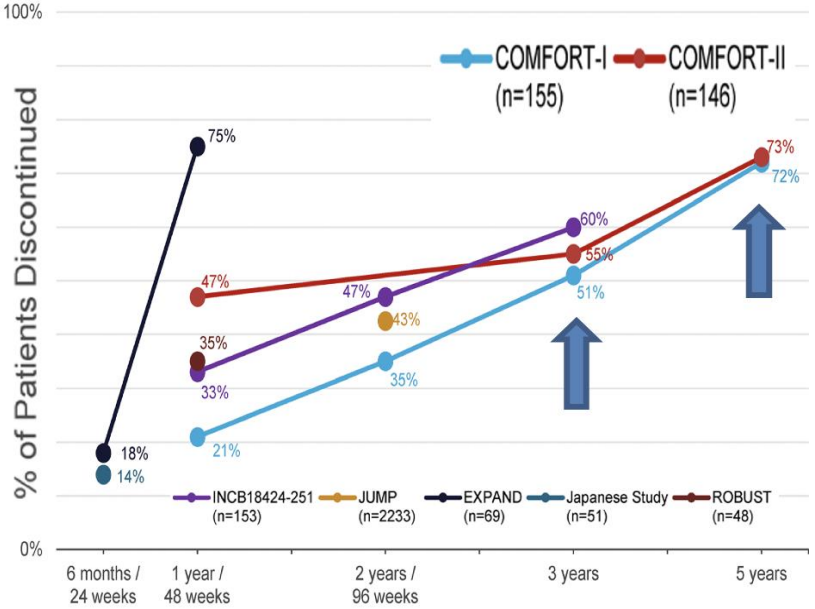
Andraos et al, Cancer Discov 2012; Guglielmelli et al, Br Journal Haematol 2016; Tvogorov et al, Sci Adv 2018; Ross et al, Haematologica 2021

RUX resistance in clinical trials

Primary resistance (ANY degree of clinical response at W24/48): 2-5%

Secondary resistance:



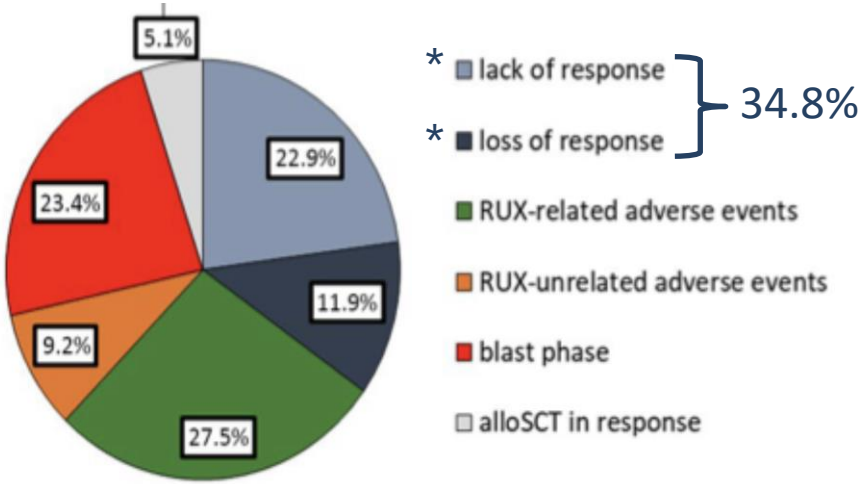


Harrison et al, Leukemia 2016; Verstovsek et al, J Hematol Oncol 2017; Passamonti&Maffioli, Blood 2018; Harrison et al, Ann Hematol 2020

RUX «failure» in the real world

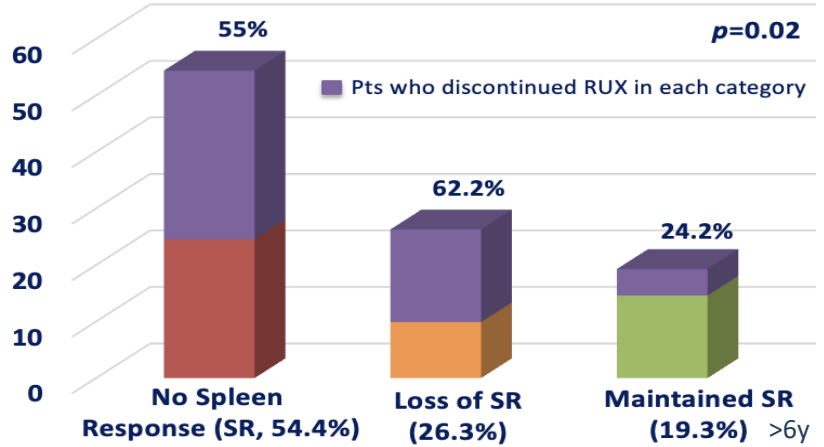
European study

524 MF, 52% int-1
41% discontinued at 3 y



Florence cohort

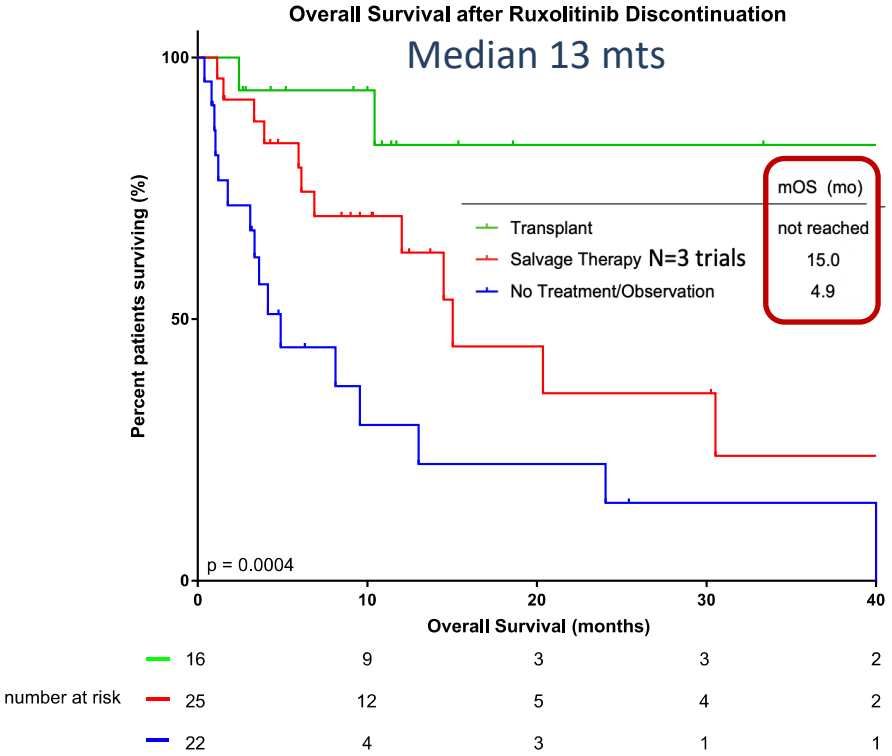
171 MF, 43% int-1
Median time to loss of SR*: 23 mts

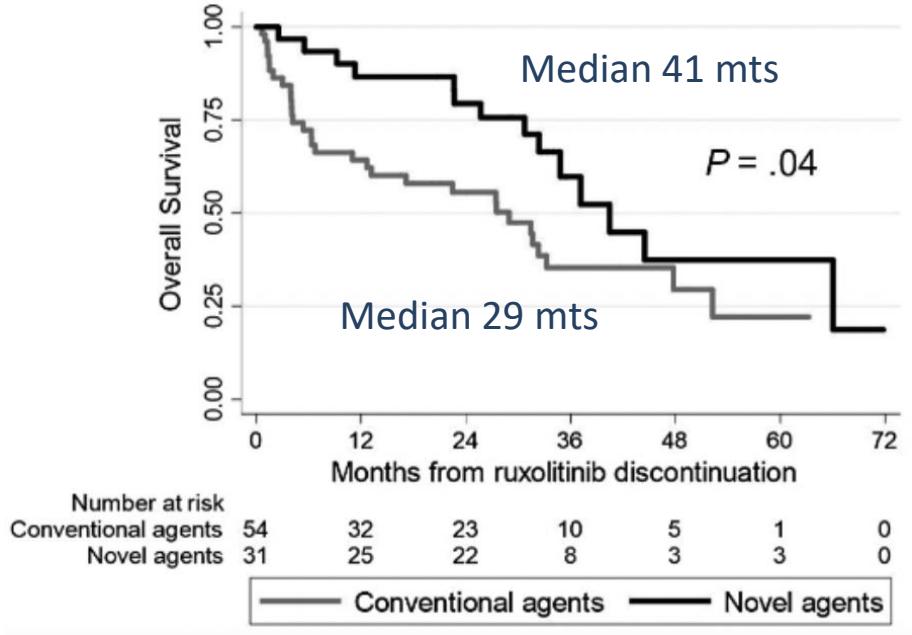


***Spleen response (SR):** for palpable spleen >10 cm, a decrease by ≥50%, stable for ≥6 mts; for spleen <10 cm, to become not palpable.
Loss of SR: re-appearance of >5 cm spleen, if the nadir was not palpable; >50% increase of spleen, if the nadir was >5 cm.

**Tefferi et al, Blood 2013; Palandri et al, Cancer 2020; Guglielmelli et al, ASH 2022*

Outcome after RUX discontinuation depends on type of salvage tx



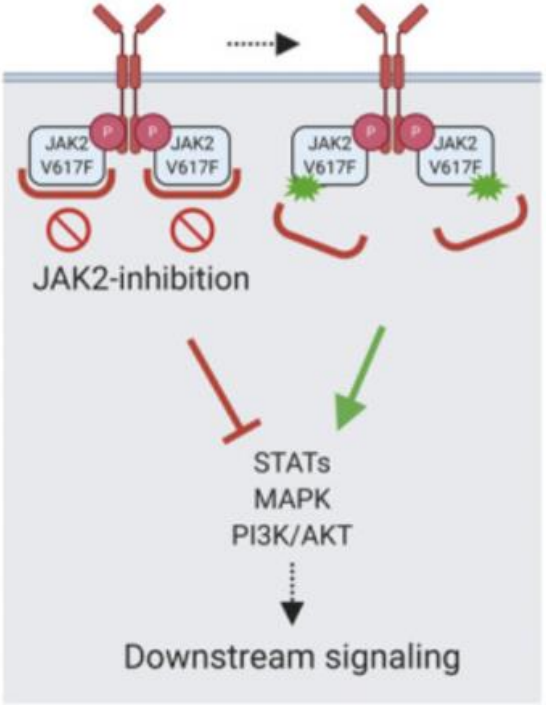


AlloSCT (N=26) and BP-evolution (N=51) excluded
Novel agents= RUX rechallenge, other JAKi, non-JAKi

Kuykendall et al, Ann Hematol 2018; Palandri et al, Cancer 2020

Possible *acquired* mechanisms of resistance to JAKi

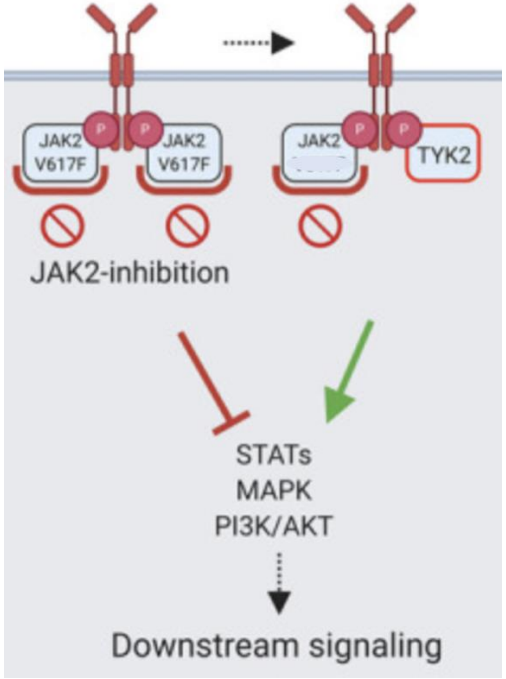
JAK resistance mutations are not observed in MF patients



- *JAK* resistance mutations occur only in vitro
- Possible explanation: insufficient selective pressure of JAKi (limited disease-modifying potential)

Hornakova et al, Haematologica 2011; Deshpande et al, Leukemia 2012; Andreoli et al, Blood 2013; Meyer SC, Hematol Oncol Clin N Am 2017; Brkic&Meyer, Hemasphere 2021; Ross et al, Haematologica 2021

Adaptive functional resistance to JAKi

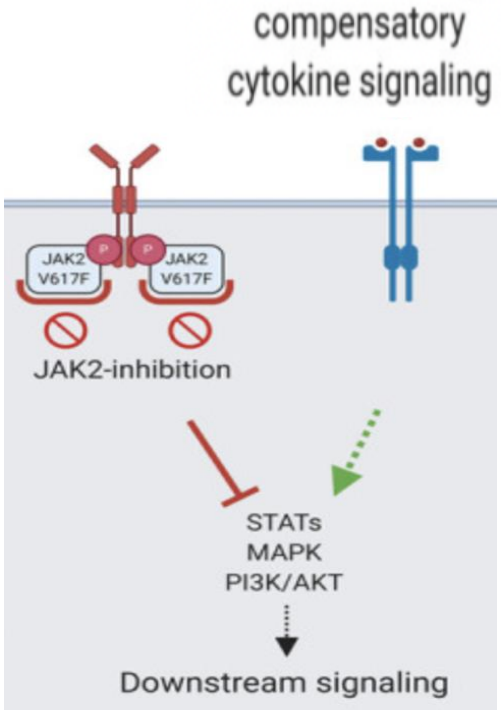


- Reactivation of JAK/STAT signaling by JAK2 family heterodimer formation (JAK1, TYK2)
- Reversible process after a drug «holiday»

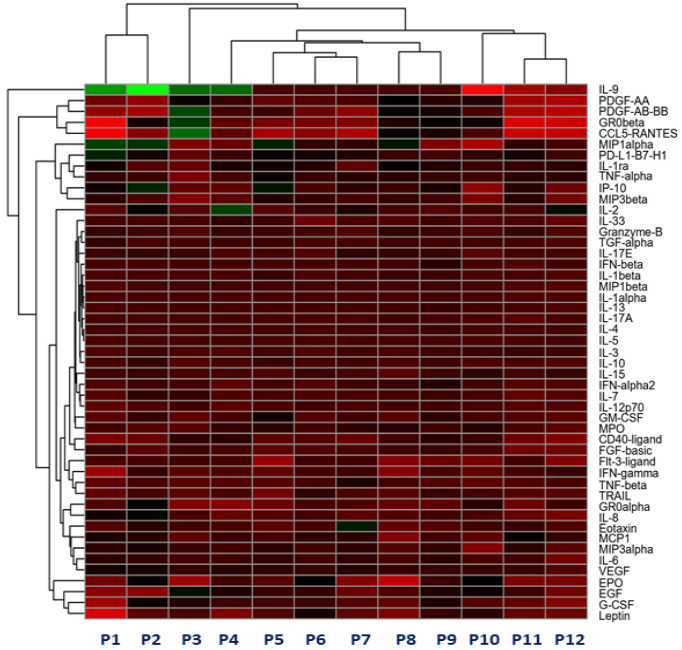
Koppikar et al, Nature 2012; Gisslinger et al, Am J Hematol 2014; Meyer SC, Hematol Oncol Clin N Am 2017; Brkic&Meyer, Hemasphere 2021

Possible *intrinsic* mechanisms of resistance to JAKi

Paracrine effects of the inflammatory microenvironment



IL-6, FGF, PDGF,…



Loss *vs*. Spleen reponse*

*Manshouri et al, Cancer Res 2011; *Tefferi et al, Blood 2013; Verstovsek et al, J Exp Med 2016; Stivala et al, J Clin Invest 2019; Brkic&Meyer, Hemasphere 2021; Guglielmelli et al, ASH 2022*

Impact of molecular landscape at baseline

	No Spleen Response (SR)*	Loss of SR*	Maintained SR	*P*
HMR at baseline (40% of 171 pts)	40.2%	51.1%	24.2%	**0.04**

Time to RUX discontinuation (weeks) based on the number of baseline myeloid-gene variants

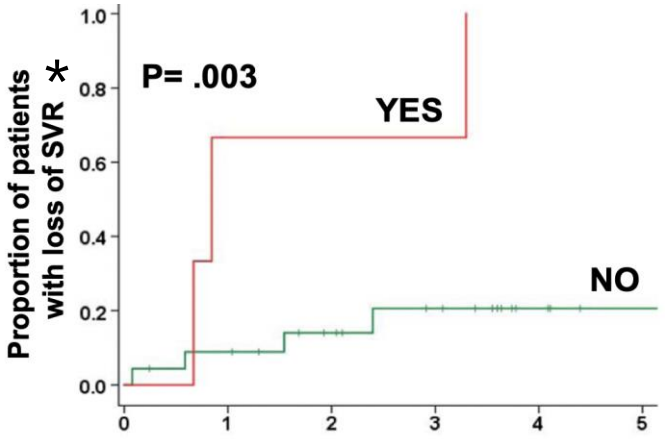
≤1 mutation (N = 53) 56%	2 mutations (N = 30) 32%	≥3 mutations (N = 12) 13%	*P* value
218 (7-369)	162 (17-387)	58 (11-137)	.001

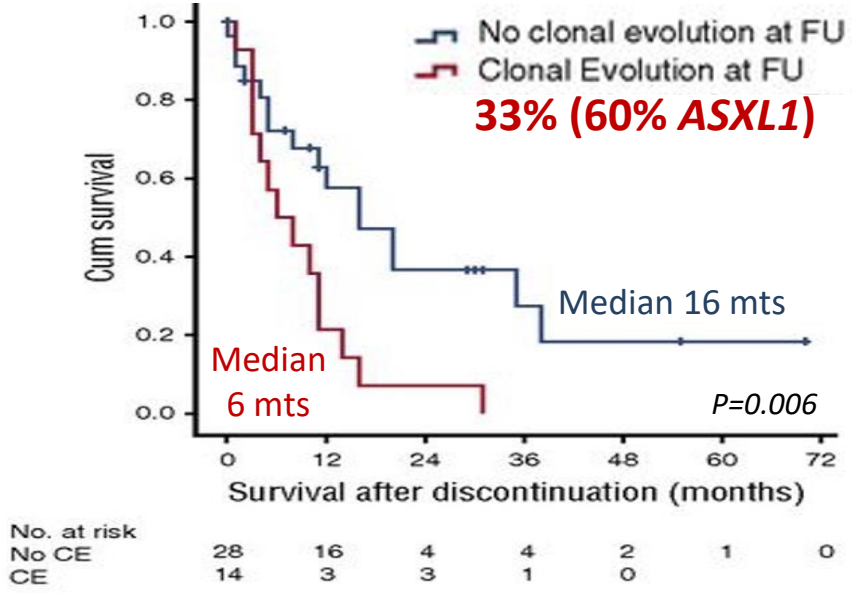
HMR: ≥1 mutated among *ASXL1*, *SRSF2*, *EZH2*, *IDH1/2*, *U2AF1*

*Tefferi et al, Blood 2013; Guglielmelli et al, Blood 2014; Patel et al, Blood 2015; Pacilli et al, Blood Cancer J 2018; Guglielmelli et al, ASH 2022

RUX does not prevent clonal evolution

Clonal evolution: 17% pts

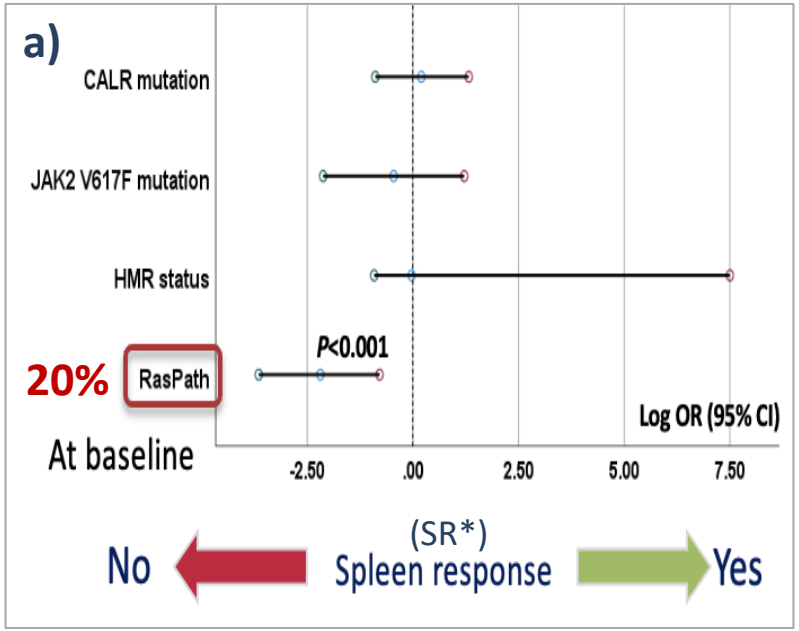




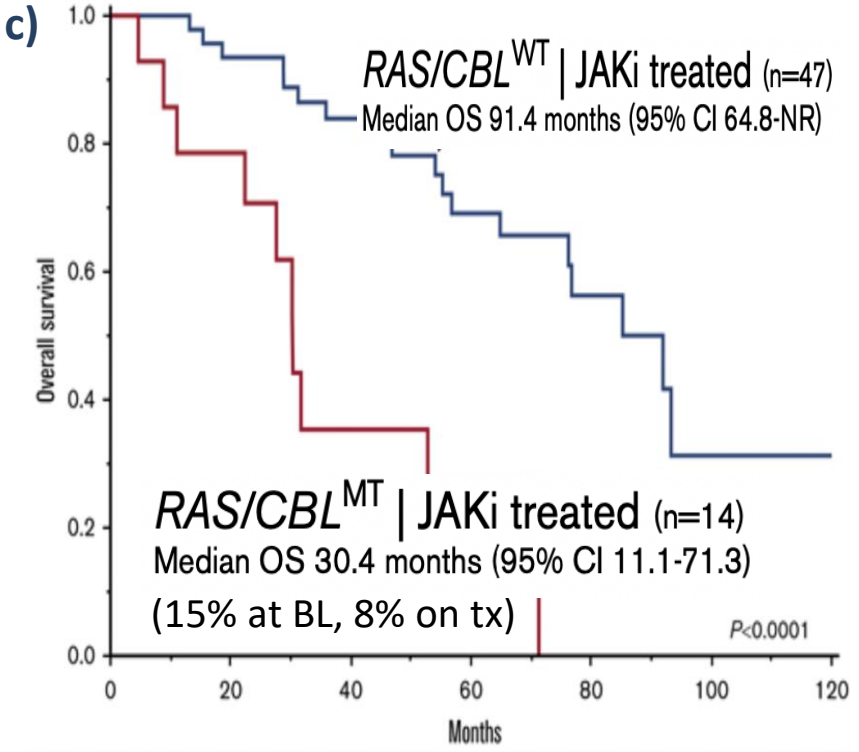
↑ variant allele frequency of myeloid-gene variants on RUX (24% pts):
↑ rate of discontinuation due to loss of spleen response*

**Tefferi et al, Blood 2013; Newberry et al, Blood 2017; Pacilli et al, Blood Cancer J 2018; Guglielmelli et al, ASH 2022*

The role of RAS/MAPK mutations



b) 50% of cases with clonal evolution at time of loss of SR*



Tefferi et al, Blood 2013; Jayavelu et al, Nature 2020; Coltro et al, Blood Adv 2020; Pandey et al, Blood Cancer J 2022; Guglielmelli et al, ASH 2022; Maslah et al, ASH 2022

RUX failure in the clinic: the problem of definitions

IWG-MRT/ELN criteria:

-Developed for clinical trials (MRI/CT)

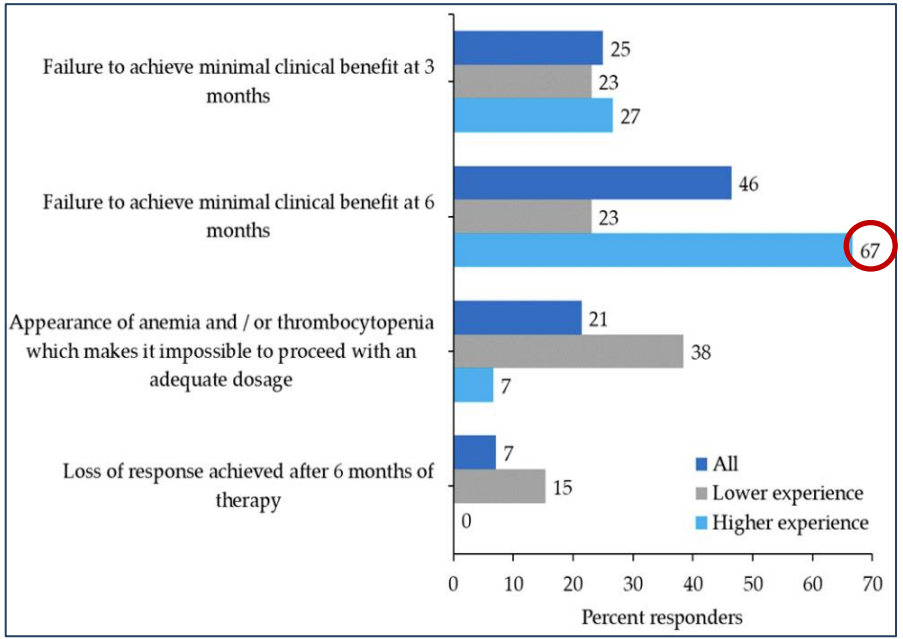
-No account for dosing/timing of drug

- Disease progression only related to ↑ splenomegaly and blast phase

NCCN guidelines:

Clinical benefit left to the clinician's discretion, even if lower than IWG-MRT/ELN criteria thresholds

Suboptimal response: a GIMEMA survey



Tefferi et al, Blood 2013; NCCN guidelines v 1.2023; Breccia et al, Curr Oncol 2022; Mascarenhas et al, Future Med 2023; Vannucchi AM, EHA 2023

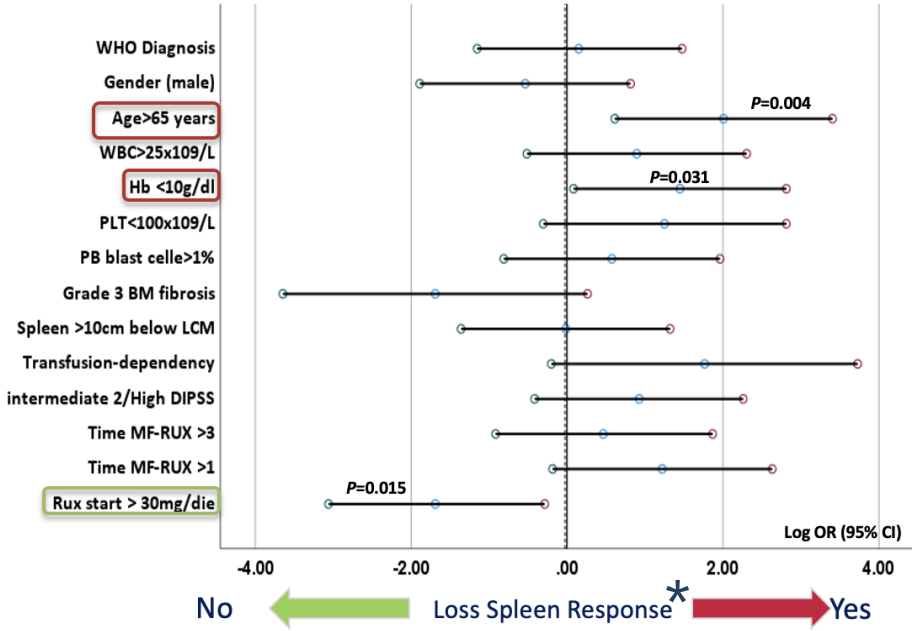
Patterns of JAKi failure: the Canadian MPN group proposal

Suboptimal spleen response	<25% reduction in spleen length after at least 3 mts of optimally dosed JAKi or persistence of a symptomatic splenomegaly
Loss of spleen response	≥50% increase in spleen length from best response
Transfusion-dependent anemia	≥4 RBC units in 8 wks occurring ≥6 mts from tx start
Severe thrombocytopenia	Unable to maintain unsupported PLT count >30-50*10^9/L if ongoing anticoagulants; and PLT count >20*10^9/L if not
Transformation to accelerated/blast phase	
Second cancers	
Infectious complications	

Gupta et al, J Clinic Oncol 2020

RUX failure in the clinic: the issue of clinical predictors

The Florence cohort



The RR6 (*Response to RUX after 6 mts)* model

Parameters	Points
RUX dose <20 mg BID at baseline, M3, M6	1
≤30% spleen length reduction at M3 & M6	1.5
RBC transfusions at M3 and/or M6	1
RBC transfusions at BL, M3, and M6	1.5

Risk	% pts	Survival (months)	HR	Score
Low	19	Not reached		0
Interm.	45	61	43-80	1-2
High	36	33	21-50	≥2.5

**Tefferi et al, Blood 2013; Maffioli et al, Blood Adv 2022; Gugliemelli et al, ASH 2022*

RUX failure in the clinic: the question of treatment switch

Consider tx switch before RUX activity exhaustion despite dose adjustment:

- if worsening of spleen size/symptoms, of blasts or of peripheral blood cells
- if persistence of a huge splenomegaly >10 cm from left costal margin even having achieved spleen length reduction >50%

Consider an appropriate RUX tapering (≥2 wks) to avoid discontinuation syndrome

Passamonti&Mora, Blood 2023; Mascarenhas et al, Future Med 2023; Vannucchi AM, EHA 2023

Possible treatment options after RUX failure

AlloSCT: if indicated by prognostic re-assessment & feasable

Other type 1 JAKi with partly different profile of target kinases

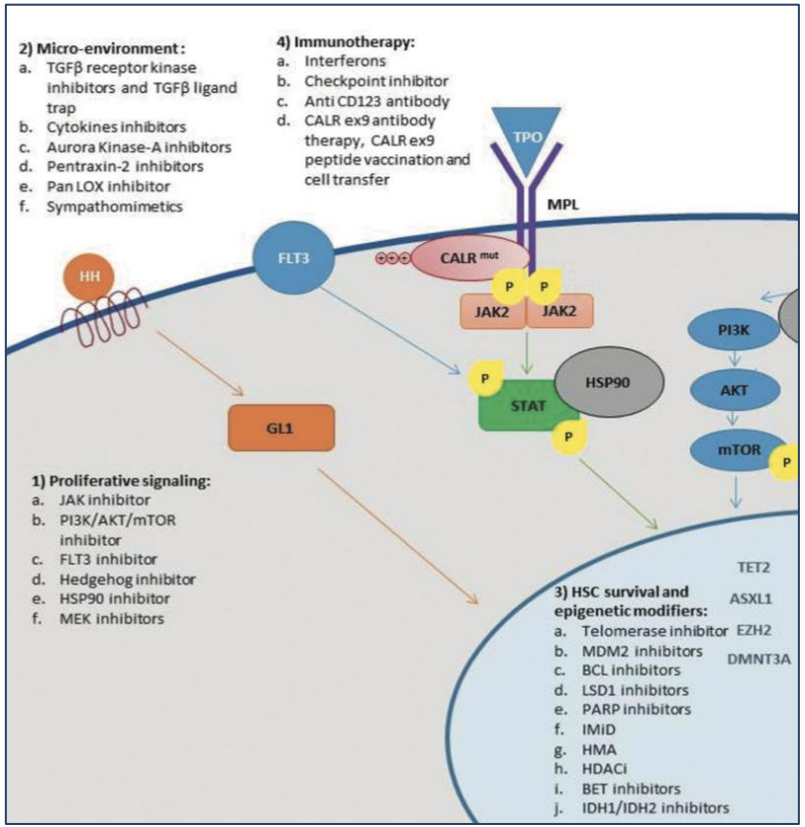
- FED (JAK2/FLT3-i): EMA approved, reference for RUX failure
- PAC (JAK2/FLT3/IRAK1/ACVR1-i)
- MMB (JAK1/JAK2/ACVR1-i)

} useful for cytopenic patients

(**RUX rechallenge:** ~50% clinical improvement, but 48% stop at 2 y)

Gupta et al, J Clinic Oncol 2020; Palandri et al, Cancer 2021; Passamonti&Mora, Blood 2023

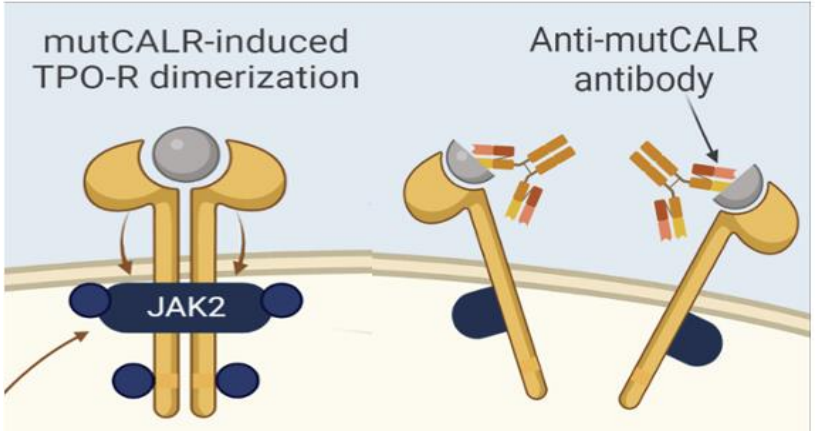
Possible treatment options to overcome JAKi resistance



Add-on to JAKi (1° or subsequent lines)

Non-JAKi

Anti-mutCALR mAb



Passamonti&Mora, Blood 2023; Reis et al, ASH 2022

Concluding remarks

JAKi have substantially transformed MF treatment and provide a rapid control of splenomegaly and symptoms

Failure of RUX is frequent after a long exposure, with an heterogeneous presentation

After RUX failure, the overarching goal for many patients may be prolongation of life, and new treatment paradigms could held a potentially meaningful impact