
# Mielofibrosi

# Le nuove terapie

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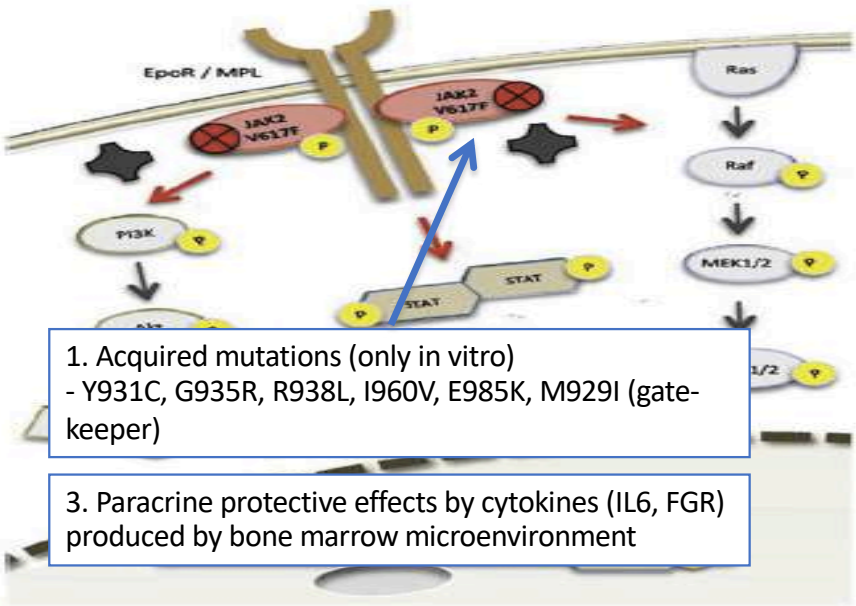
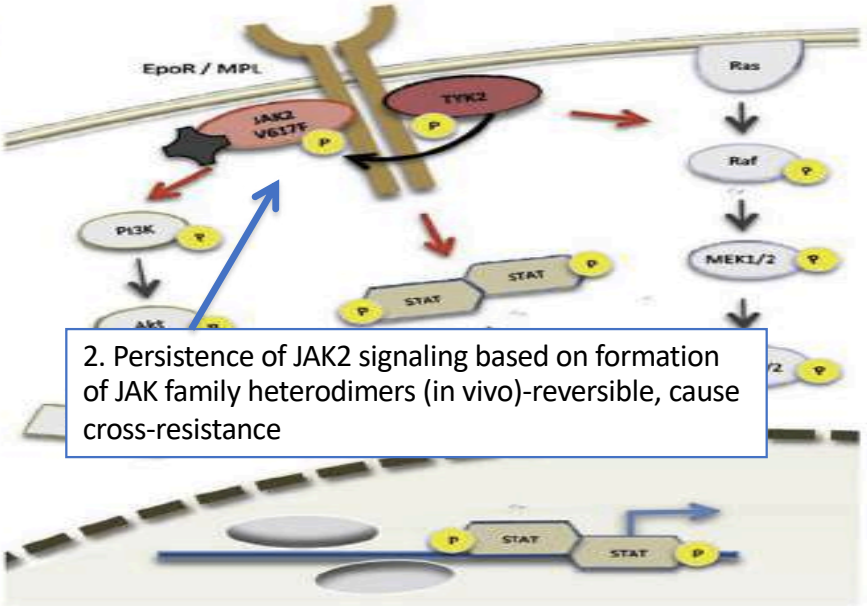
# Resistance to JAK2 inhibitors

- Not yet defined
- Primary resistance has been observed in few patients (less than 2-5%)
- Secondary resistance:




1. Acquired mutations (only in vitro)
- Y931C, G935R, R938L, I960V, E985K, M929I (gate-keeper)

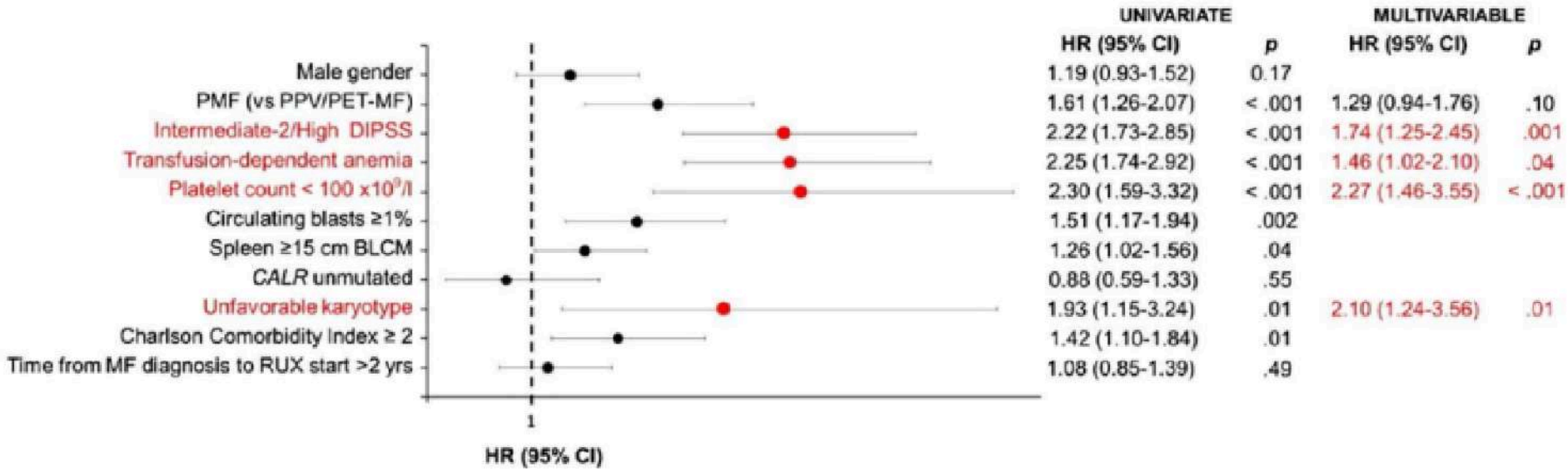
3. Paracrine protective effects by cytokines (IL6, FGR) produced by bone marrow microenvironment




2. Persistence of JAK2 signaling based on formation of JAK family heterodimers (in vivo)-reversible, cause cross-resistance

Meyer SC Hematol Oncol Clin N Am 2017

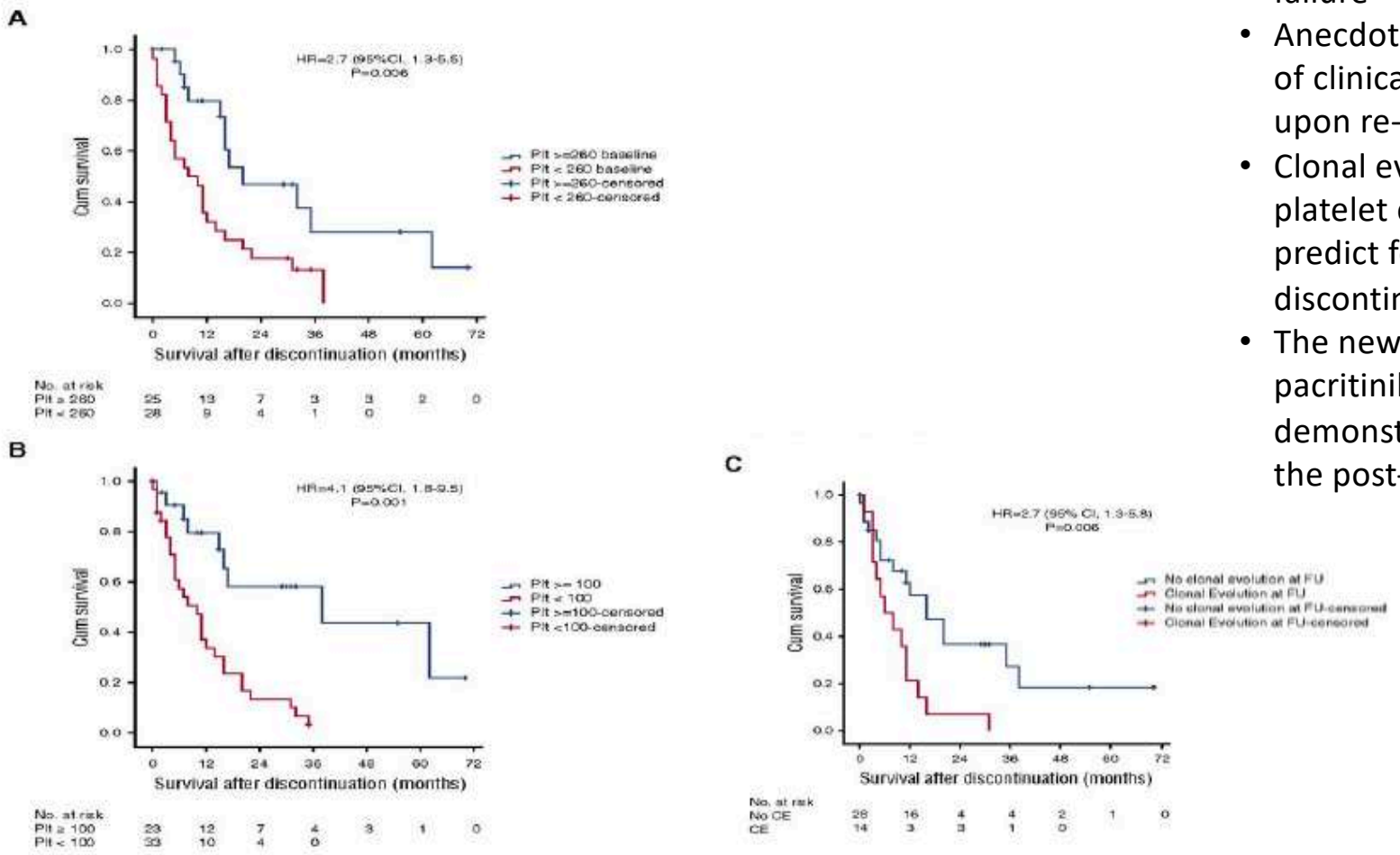
# Life after ruxo in MF patients




- After a median FU of 37 months, **51% of patients discontinued ruxo (40.8% at 3 years)**
- The probability to stop ruxolitinib is higher in patients with advanced phase of disease
- OS is higher for pts who stopped with loss of response as compared to lack of response
- Use of investigational drugs improves OS after discontinuation of ruxo

Palandri et al Cancer 2020

# Outcome after ruxolitinib: OS 14 months




- Unmeet need: definition of ruxo failure
- Anecdotal reports of restoration of clinical responsiveness to ruxo upon re-challenge
- Clonal evolution and worsening platelet counts while on ruxo predict for worse OS upon discontinuation
- The new inhibitors (fedratinib, pacritinib, momelotinib) have demonstrated some efficacy in the post-ruxo setting

Newberry at al, Blood 130(9):1125-1131

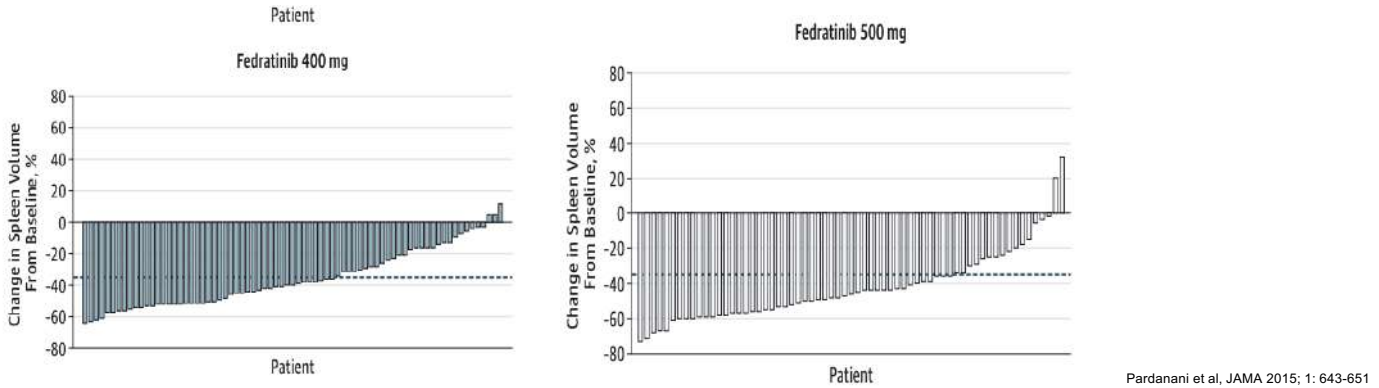
# Fedratinib in MF

- Fedratinib is an oral kinase inhibitor with activity against wild-type and mutationally activated *JAK2* and FMS-like tyrosine kinase 3 (*FLT3*)
- Fedratinib has a half-maximal enzyme inhibitory concentration ($IC_{50}$) value for wild-type JAK2 and JAK2-V617F (3 nM) that is 35 times lower than that for JAK1, > 300 times lower than that for JAK3, and > 100 times lower than that for TYK2
- Fedratinib is a more selective inhibitor of JAK2 than ruxolitinib and has a longer effective half-life (~ 41 h vs. 3 h, respectively), which allows more persistent JAK2 inhibition and once-daily dosing

Pardanani et al, JAMA 2015; 1: 643-651

# Fedratinib in MF: JAKARTA-1 trial

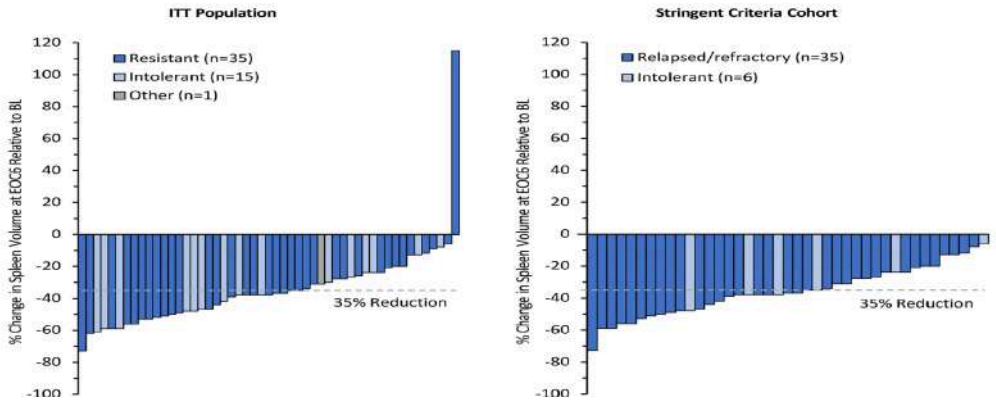
- Double blind, randomized, placebo-controlled phase 3 study
- 289 pts interm2/high risk MF were enrolled and randomized to fedratinib 400 mg or 500 mg vs placebo for at least 6 consecutive 4-week cycles
- Primary endpoint: spleen response (>35% reduction in spleen volume from baseline)
- Endpoint achieved by 36% of pts with 400 mg and 40% in 500 mg vs 1% with placebo. Symptom response in 36% and 34%, respectively.
- Common AEs: anemia, gastrointestinal symptoms, and increased levels of liver transaminases, serum creatinine, and pancreatic enzymes. Encephalopathy was reported in 4 women who received fedratinib 500 mg/d. A diagnosis of Wernicke encephalopathy was supported by magnetic resonance imaging in 3 cases and suspected clinically in 1 case.




Pardanani et al, JAMA 2015; 1: 643-651

# Fedratinib in MF: JAKARTA-2 trial

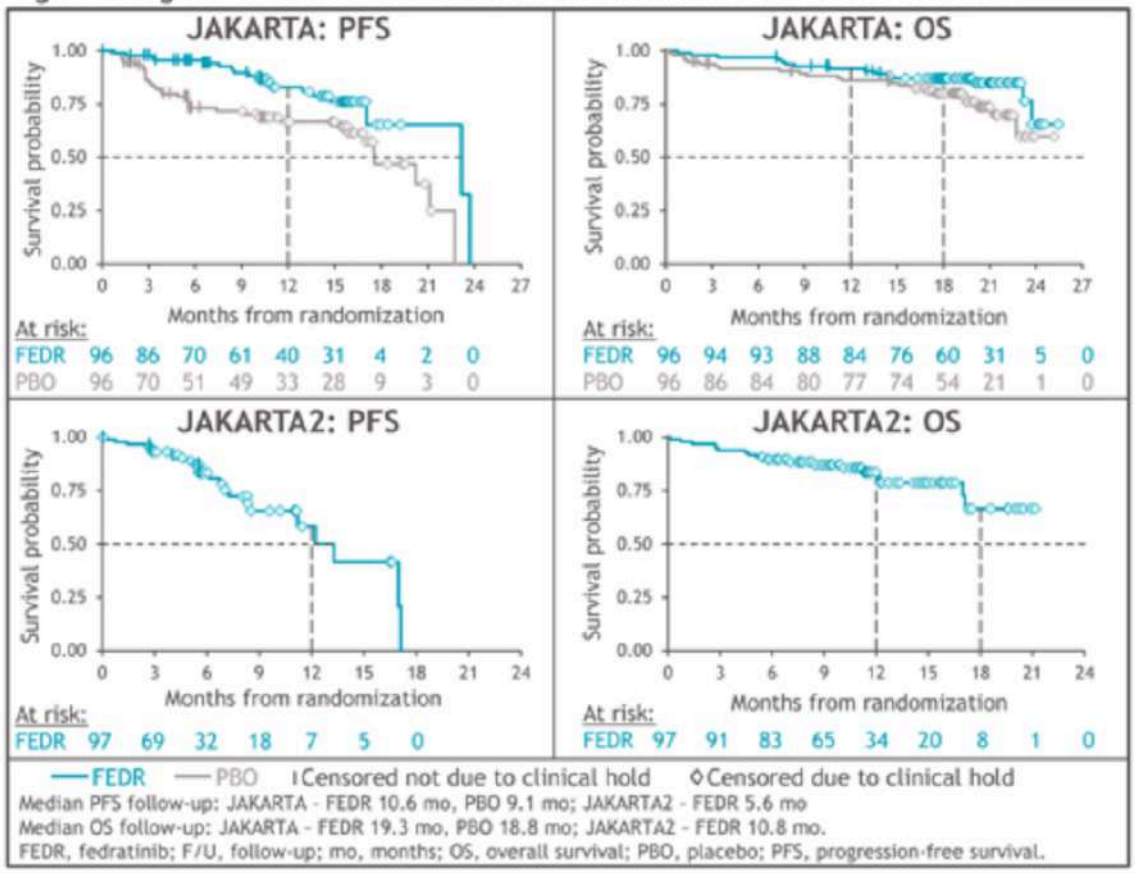
- Single-arm, open-label, non-randomised, phase 2, multicentre study
- 97 pts resistant/intolerant to ruxolitinib with int2/high risk
- Patients received oral fedratinib at a starting dose of 400 mg once per day, for six consecutive 28-day cycles. The primary endpoint was spleen response (defined as the proportion of patients with a ≥35% reduction in spleen volume as determined by blinded CT and MRI at a central imaging laboratory).
- "Per protocol" analysis showed 55% spleen volume response (53% in pts with stable or no response during ruxo, 38% in pts with disease progression and 61% in those with a loss of response)
- Recently an ITT analysis was performed: spleen volume response 31% and symptoms control in 27%. Median duration of spleen response was not reached.




Harrison et al Lancet Hematol 2017; 4: 317-324

# Fedratinib in MF: PFS and OS

Figure. Progression-free survival and overall survival in JAKARTA and JAKARTA2

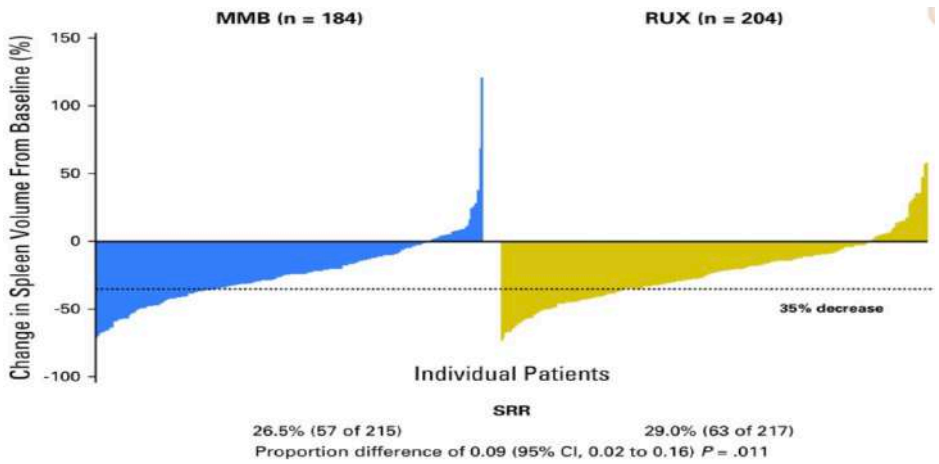


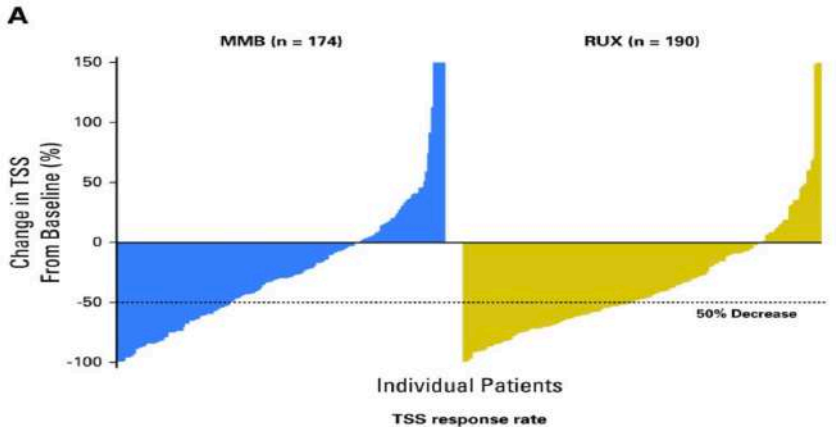

Median PFS follow-up: JAKARTA - FEDR 10.6 mo, PBO 9.1 mo; JAKARTA2 - FEDR 5.6 mo
Median OS follow-up: JAKARTA - FEDR 19.3 mo, PBO 18.8 mo; JAKARTA2 - FEDR 10.8 mo.
FEDR, fedratinib; F/U, follow-up; mo, months; OS, overall survival; PBO, placebo; PFS, progression-free survival.

Harrison et al EHA 2021

# Momelotinib in MF: Simplify-1 trial

- 432 pts interm2/high risk or symptomatic int1 MF were enrolled and randomized to momelotinib 200 mg or ruxo 20 mg BID for 24 weeks
- Primary endpoint: spleen response (>35% reduction in spleen volume from baseline)
- Endpoint achieved by 26.5% of pts with momelotinib 200 mg and 29% in ruxo arm
- A >50% of reduction in TTS was observed in 28.4% vs 42% in momelotinib and ruxo arms, respectively. Transfusion independence was improved with momelotinib
- Common AEs: anemia, thrombocytopenia, infections (7% with momelotinib), neuropathy (10% with momelotinib all grade <2)

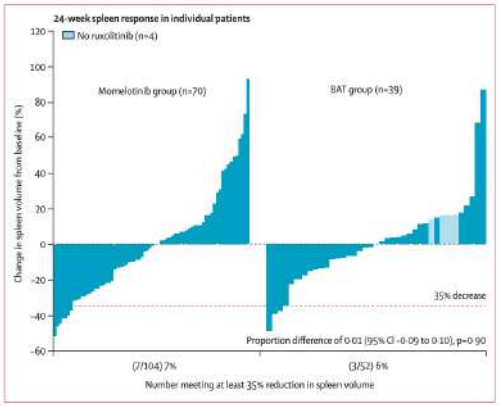


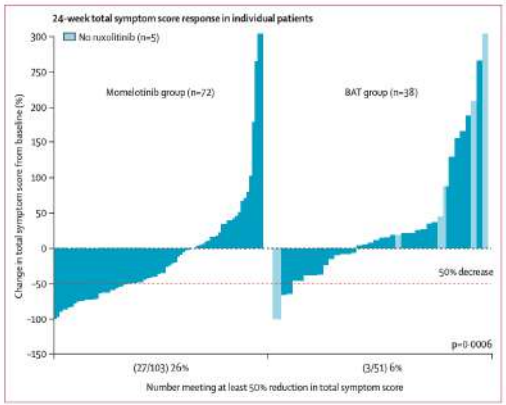




Mesa et al J Clin Oncol 2017; 35: 3844-3850

# Momelotinib in MF: Simplify-2 trial

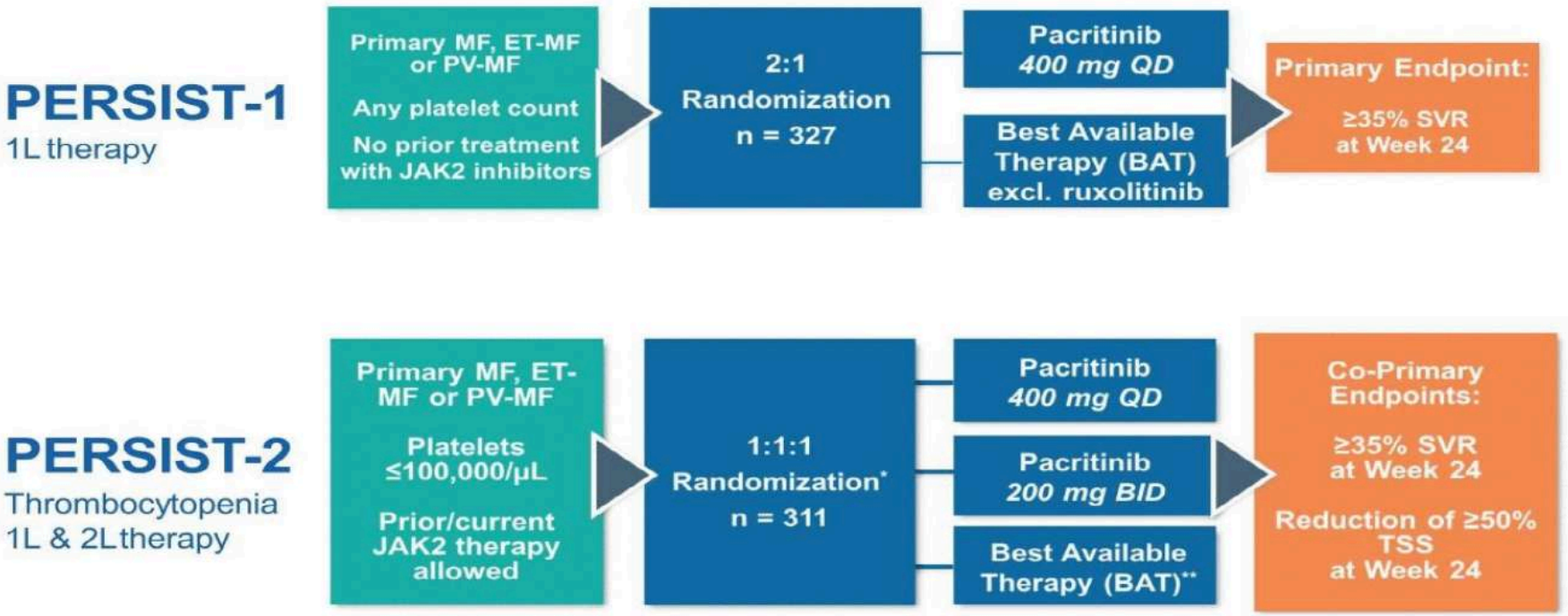
- Phase 3 trial vs BAT: patients who had MF and previous ruxolitinib treatment for at least 28 days who either required red blood cell transfusions while on ruxolitinib or ruxolitinib dose reduction to less than 20 mg twice a day with at least one of grade 3 thrombocytopenia, anaemia, or bleeding at grade 3 or worse, with palpable spleen of at least 5 cm and without grade 2 or greater peripheral neuropathy were included in the study.
- 156 pts enrolled (2:1): 73 (70%) of 104 patients in the momelotinib group and 40 (77%) of 52 patients in the BAT group completed the 24-week treatment phase.
- 7% patients in the momelotinib group and 6% in the BAT group had a reduction in the spleen volume by at least 35% compared with baseline
- The most common grade 3 or worse adverse events were anaemia (14 [14%] of 104 in the momelotinib group vs seven [14%] of 52 in the BAT group), thrombocytopenia (seven [7%] vs three [6%]), and abdominal pain (one [1%] vs three [6%]). Peripheral neuropathy occurred in 11 (11%) of 104 patients receiving momelotinib.



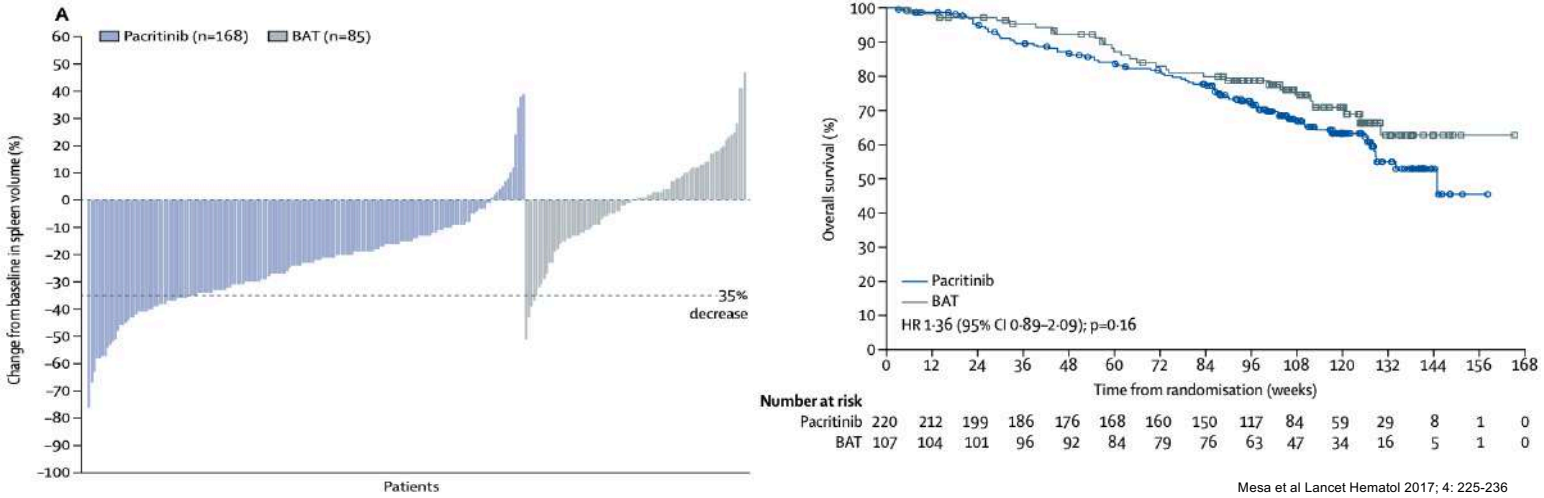

Harrison et al Lamcet Hematol 2018; 5: 73-81

# Pacritinib


PERSIST-1
1L therapy
Primary MF, ET-MF or PV-MF
Any platelet count
No prior treatment with JAK2 inhibitors
2:1 Randomization n = 327
Pacritinib 400 mg QD
Best Available Therapy (BAT) excl. ruxolitinib
Primary Endpoint:
≥35% SVR at Week 24
PERSIST-2
Thrombocytopenia
1L & 2L therapy
Primary MF, ET-MF or PV-MF
Platelets ≤100,000/μL
Prior/current JAK2 therapy allowed
1:1:1 Randomization* n = 311
Pacritinib 400 mg QD
Pacritinib 200 mg BID
Best Available Therapy (BAT)**
Co-Primary Endpoints:
≥35% SVR at Week 24
Reduction of ≥50% TSS at Week 24

# Pacritinib in MF: Persist-1 trial

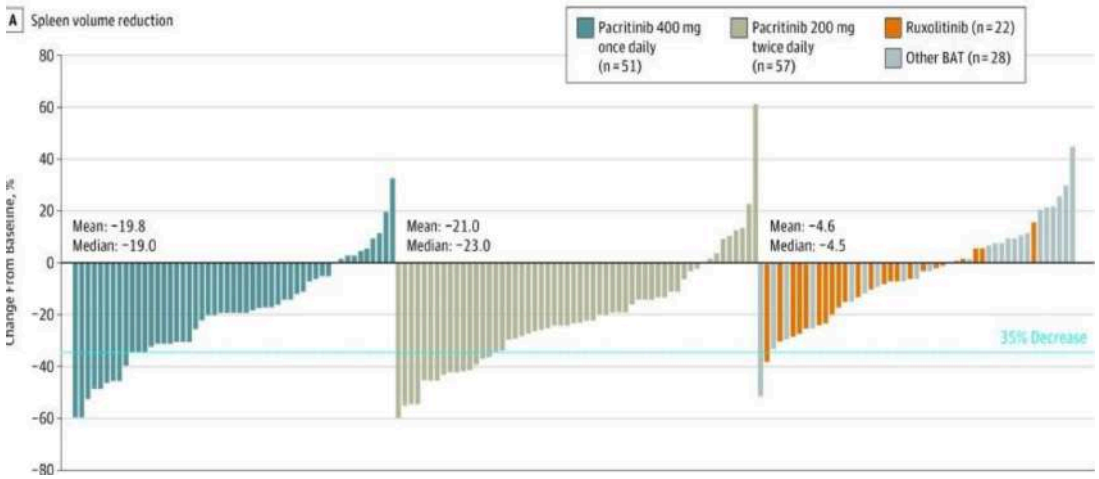
- Phase 3 randomized vs BAT (excluding ruxo)
- 327 pts enrolled and randomized to pacritinb 400 mg QD or BAT (2:1)
- Primary endpoint was spleen volume reduction > 35% at week 24
- Spleen volume reduction 19% pacritinib vs 5% BAT arm
- The most common side effects were anemia, thrombocytopenia, diarrhea, increased risk of cardiac failure (5%)




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

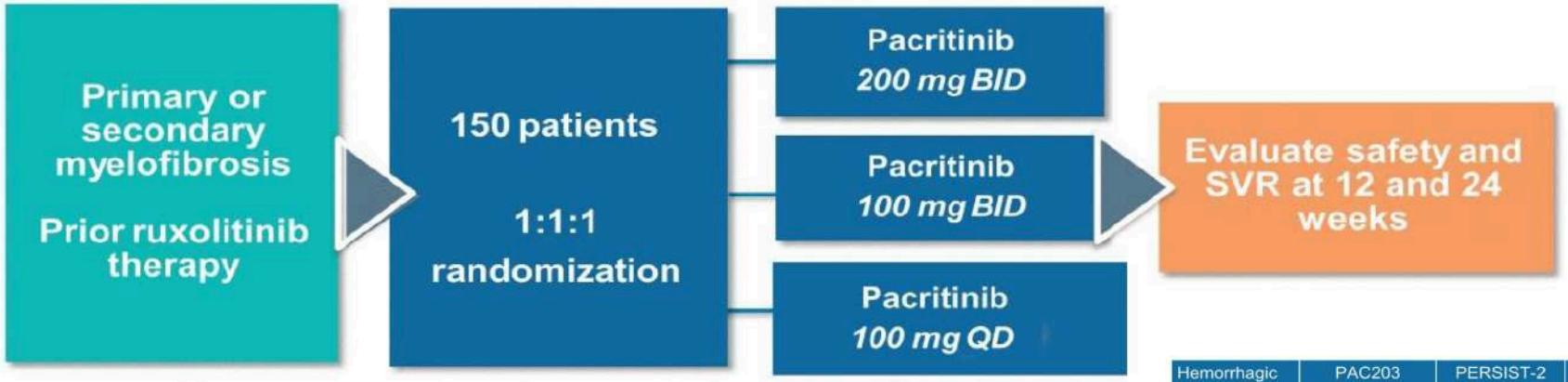
# Pacritinib in MF: Persist-2 trial

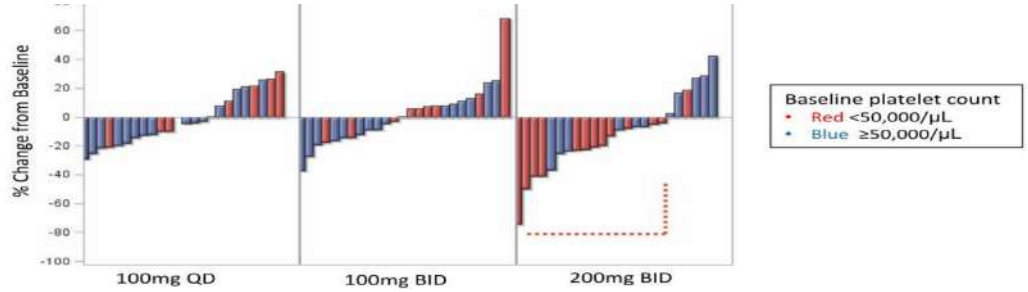
- Phase 3 randomized vs BAT
- 311 pts enrolled and randomized to pacritinb 400 mg QD, 200 mg BID or BAT (48% previously treated with ruxo) with plt count ≤ 100 x $10^9$/L
- Co-primary endpoints were spleen volume reduction > 35% and 50% or more reduction in TSS at week 24
- Spleen volume reduction 18% pacritinib vs 3% BAT arm; TSS 25% vs 14%. More responses in pacritinib BID arm (even for transfusion dependence)
- The most common side effects were gastrointestinal adverse events, fatigue, peripheral edema, and dizziness




Mascarenhas et al JAMA 2018; 4: 652-659

# Pac203 trial



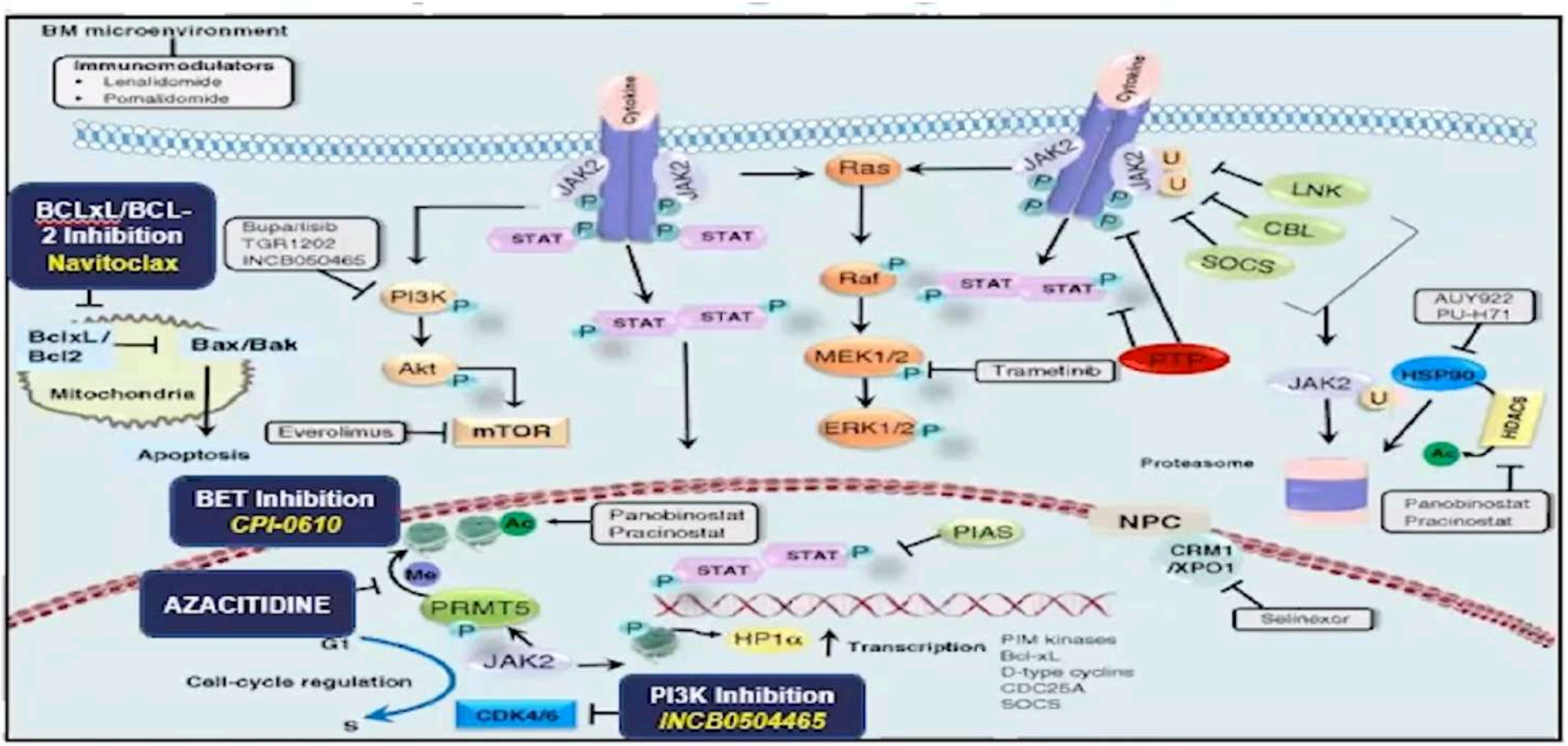

| Hemorrhagic Events (%) | PAC203 Pacritinib 200mg BID (N=54) | PERSIST-2 Pacritinib 200mg BID (N=106) | PERSIST-2 BAT (N=98) |
|---|---|---|---|
| Grade 3 | 5.6 | 14.2 | 7.1 |
| Grade 4 | 0 | 0 | 1.0 |
| Grade 5 | 1.9 | 1.9 | 0 |

| Cardiac Events (%) | PAC203 Pacritinib 200mg BID (N=54) | PERSIST-2 Pacritinib 200mg BID (N=106) | PERSIST-2 BAT (N=98) |
|---|---|---|---|
| Grade 3 | 3.7 | 4.7 | 5.1 |
| Grade 4 | 0 | 1.9 | 2.0 |
| Grade 5 | 0 | 0 | 4.1 |

SVR rates were highest with 200 mg twice per day (100 mg once per day, 0%; 100 mg twice per day, 1.8%; 200 mg twice per day, 9.3%), particularly among patients with baseline platelet counts <50 × 103/µL (17%; 4 of 24).

Gerds et al Blood Adv 2020

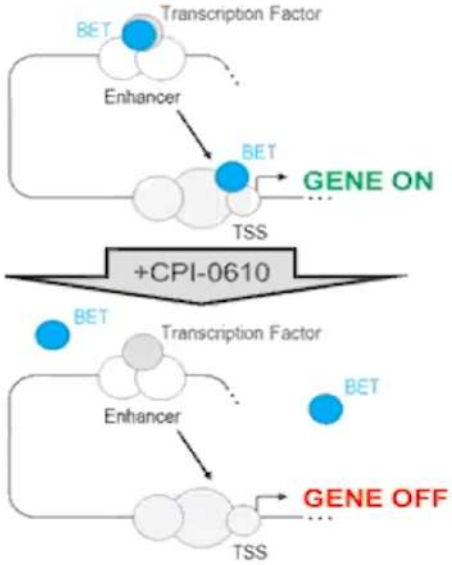
# Possible future approaches in combination



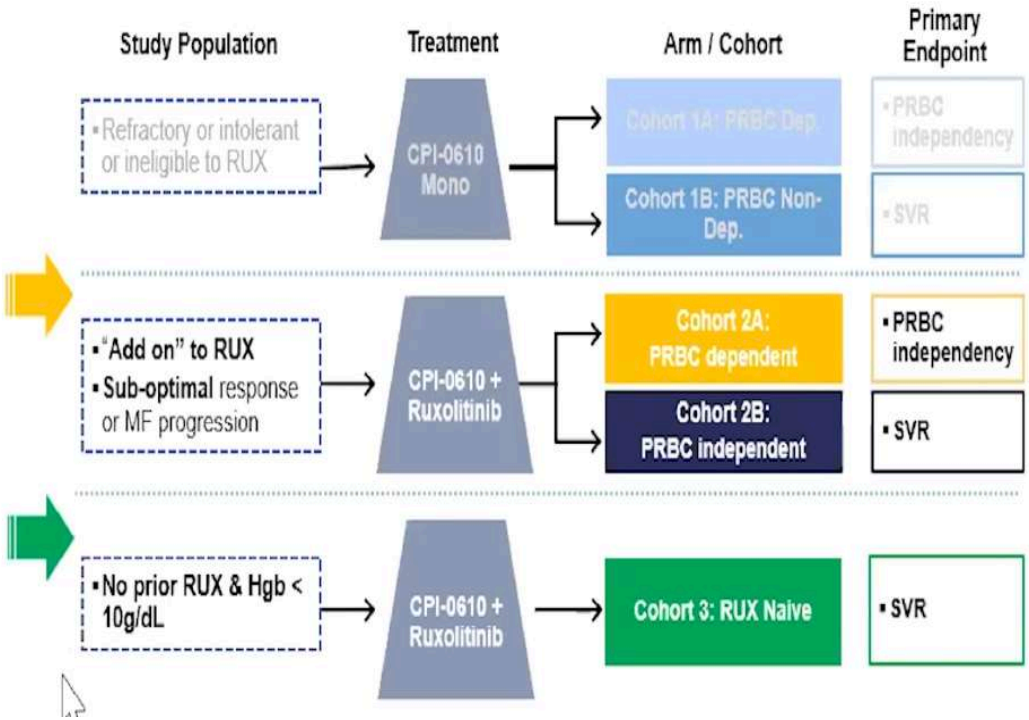
# Bromodomain inhibitor (BET): CPI-0610 or Pelabresib

- By inhibition of BET proteins:
- downregulation of pro-inflammatory cytokines via NF-kB pathway
- Inhibition of megakaryocyte differentiation
- Inhibition of TGF-B target genes

- CPI-0610
- potent, selective, best-in-class BET inhibitor
- Enhance the efficacy of ruxo, with antiproliferative and antifibrotic effects



# MANIFEST trial: CPI-0610 alone or add-on to ruxolitinib




- **ARM1 (monoTx in advanced phase)**

- 27 nTD patients

SVR > 35% 23.8% at 24 weeks

TSS> 50%  47.4%

- 16 TD patients

21.4% converted to TI

SV change -17.4% at week 24

TSS >50% 8.3%

- **ARM2 (add-on in SoR)**

-26 nTD patients

SVR >35% 29%

TSS >50%  38%

- 44 TD patients

SVR > 35% 21%

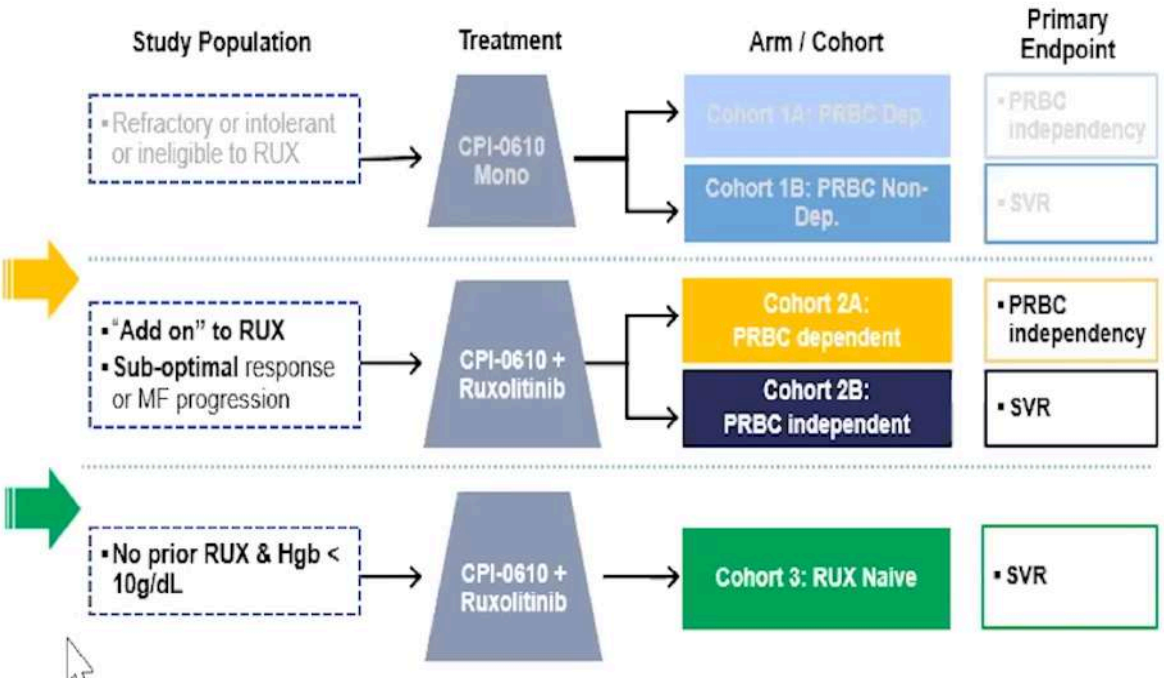
TSS > 50% 46%

34.4% converted to TI

- 41% bone marrow fibrosis improvement

Verstovsek et al, ASH 2020: 56; Talpaz et al ASH 2020: 2163

# MANIFEST trial: CPI-0610 add-on to ruxolitinib in naive pts




- **ARM3 (add-on in naïve pts)**
- 78 patients

SVR >35% 67%
TSS >50% 57%

33% achieved at least one grade of BM fibrosis improvement

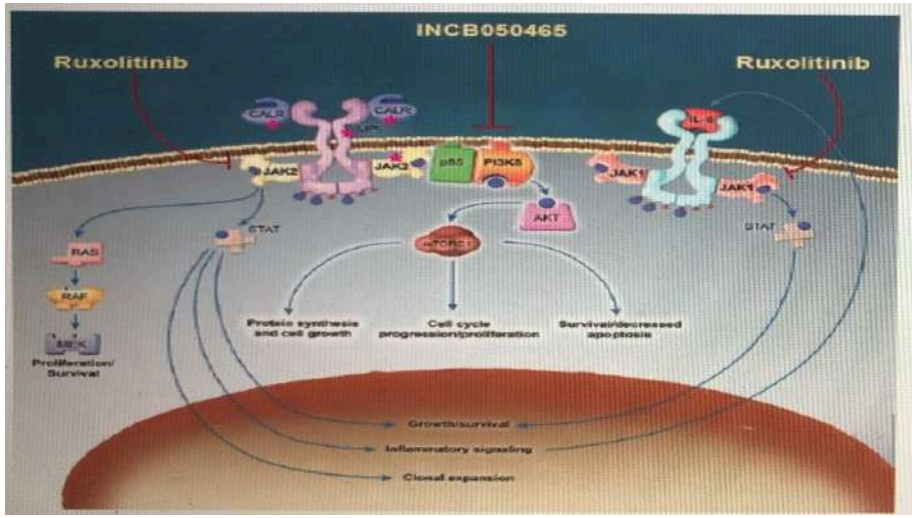
No correlation between SV, plts count and responses

Safety

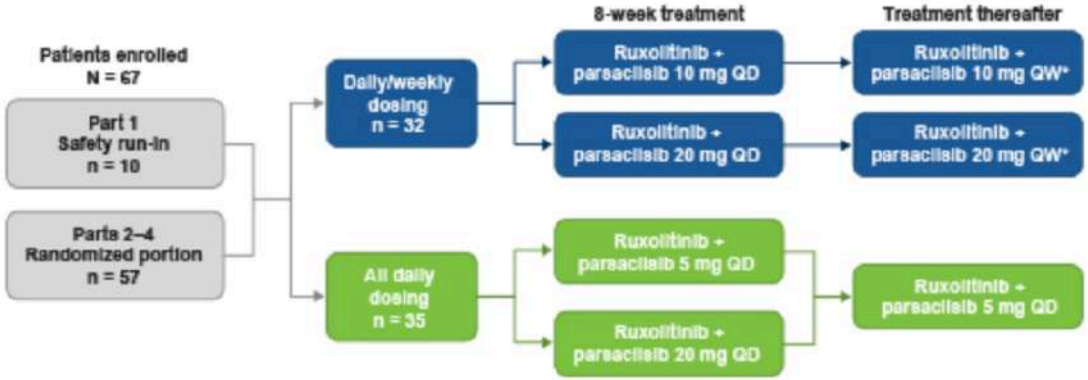
Hematological toxicity (anemia 33%)
Diarrhea (30%)
Respiratory tract infections
Nausea
Abdominal pian

Mascarenhas et al ASH 2020: 55

# Parsaclisib in ruxo R/R MF patients




- A novel potent and highly selective PI3Kδ inhibitor with favourable once daily dosing
- Phase 2 study in MF with plts > 50 x $10^9$/L with suboptimal response on ruxo for more than 6 months with stable dose for more than 8 weeks and palpable spleen (>10 cm or >5 with symptoms)



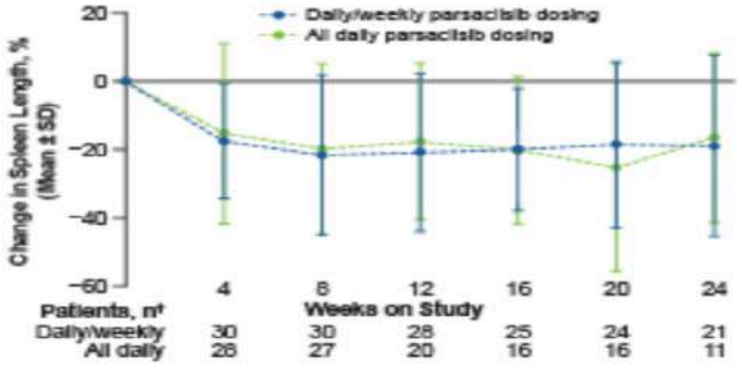

Yacoub et al EHA 2020 abstract 432

# Parsaclisib: results

A

| Response Category, n (%) | Daily/Weekly Dosing | All Daily Dosing |
|---|---|---|
| **Week 12** | **n = 29** | **n = 27** |
| ≥10% to <25% reduction | 8 (28) | 11 (41) |
| ≥25% to <35% reduction | 1 (3) | 3 (11) |
| ≥35% reduction | 0 | 1 (4) |
| **Week 24** | **n = 29** | **n = 23** |
| ≥10% to <25% reduction | 2 (7) | 6 (26) |
| ≥25% to <35% reduction | 3 (10) | 5 (21) |
| ≥35% reduction | 1 (3) | 2 (9) |

B




- 67 patients enrolled
- Median duration of ruxo: 28 weeks
- Evaluable for spleen response: 56 pts

- Discontinued 38% (11% for AEs, more for pts with daily/weekly dosing 54% compared to all daily dosing 5%)
- Thrombocytopenia (39% vs 30%)
- Diarrhea
- Nausea
- Fatigue
- Back pain
- Dyspnea

Yacoub et al EHA 2020 abstract 432

# Bomedemstat (IMG-7289 as inhibitor of LSD1-Lysine-specific demethylase 1)

- LSD1 is a histone H3K4 demethylase critical for self renewal of malignant cells
- LSD1 bound to GF11b and allows maturation of megakaryocytes

- 40 patients: 45% primary MF, 55% secondary MF
- Median age 68 years, 58% males (65% up to 4 previous therapies)

- 37% transfusion dependant (TD), 75% > 2 mutations (43% ASXL1 and U2AF1)

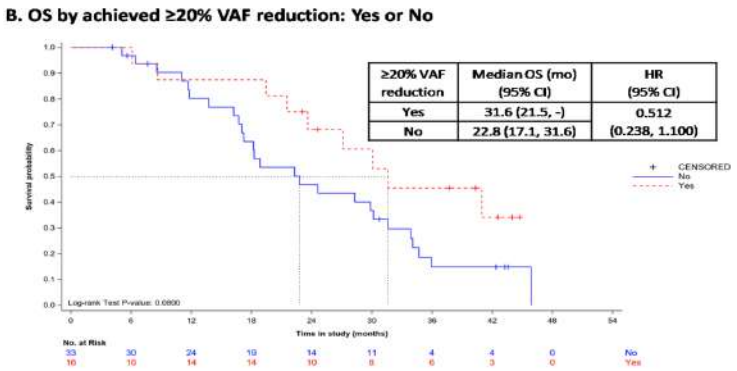
- 86% reduced symptoms (TSS >50% about in 30%)
- 10 pts evaluable in phase 2: SVR 100% (about 20% SVR>35%)

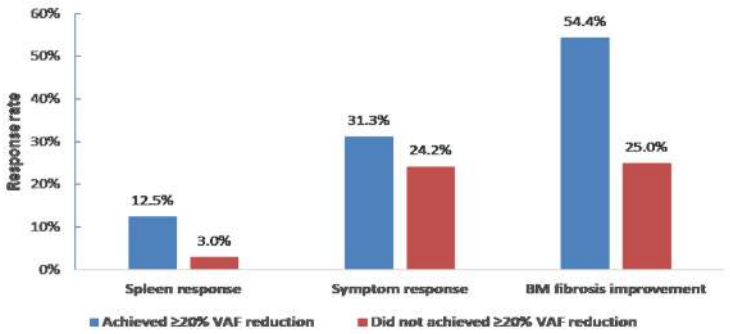
- 70% of pts have stable or increased Hb level

Yacoub et al ASH 2020 abstract 51

# Imetelstat: ImBark trial

- Phase 2 study (9.4 vs 4.7 mg/Kg) in 107 int2/high risk MF relapsed/refractory to prior JAK2 inhibitor
- In the 9.4 mg/Kg arm the responses are higher with TSS>50% 32.2% (vs 6.3% of 4.7 mg/Kg) and with a median OS of 28.1 months (vs 19.9 months)
- Imetelstat seems to have impact on biological modifications: 5/24 pts with abnormal karyotype achieved >50% reduction in cytogenetic clone (all with 13q-). Increased dose of imetelstat have an impact on VAF reduction (46.2% vs 17.4%) that correlate with increased spleen responses, TSS>50%, bone marrow fibrosis improvement (54.4%) and increased OS (3-y OS 45.5% vs 14.9%).

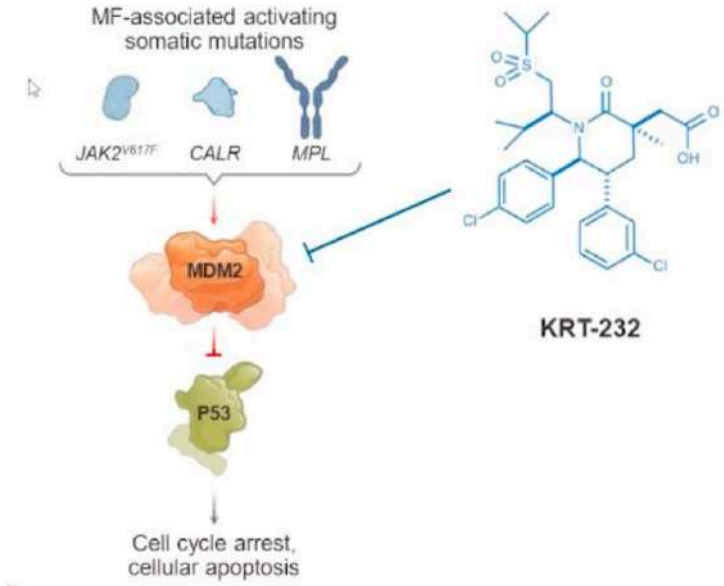


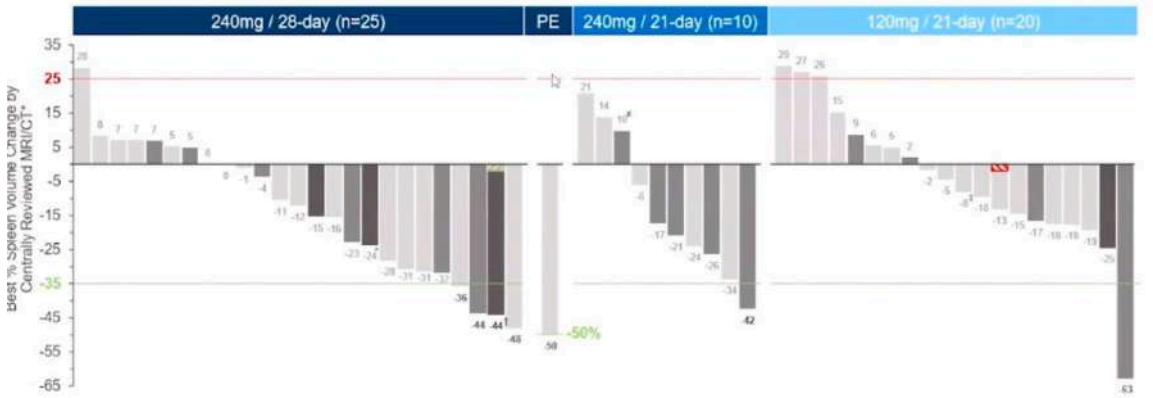




Mascarhenas et al ASH 2020: 53 and 346

# KRT-232: a novel MDM2 inhibitor

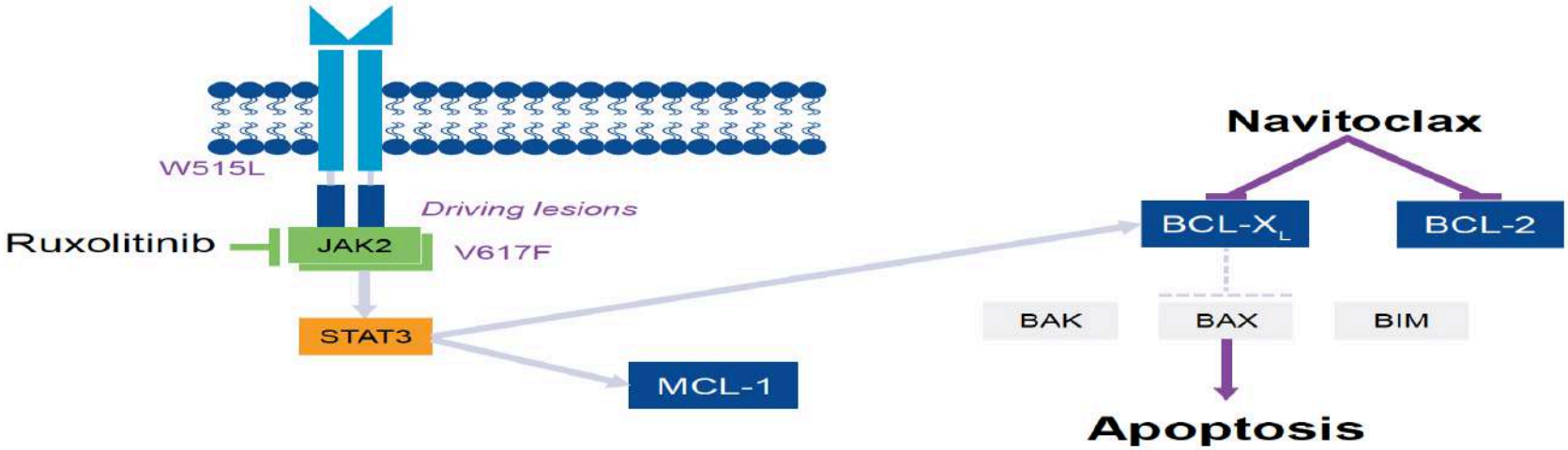
- Phase 2 study: once-daily dosing of KRT-232 at 240 mg (Day 1-7 of 28-day cycle) yielded a best spleen volume reduction (SVR) ≥35% by central review in 16% of pts, best total symptom score (TSS) response > 50% in 30% of pts, and 87% reduction of CD34+ cells in peripheral blood at Week 24. Spleen responses were superior in pts who were off RUX vs those on RUX at baseline imaging (best SVR ≥35%: 29% vs 0%).
- BOREAS trial is ongoing: randomized (2:1) to KRT-232 (240 mg on Day 1-7/28-day cycle; n = 188) or best available treatment (BAT; n = 94) and stratified by MF type (primary vs secondary) and baseline TSS (≤10 vs > 10).




Al-Ali et al EHA 2020; Verstovsek et al ASCO 2021

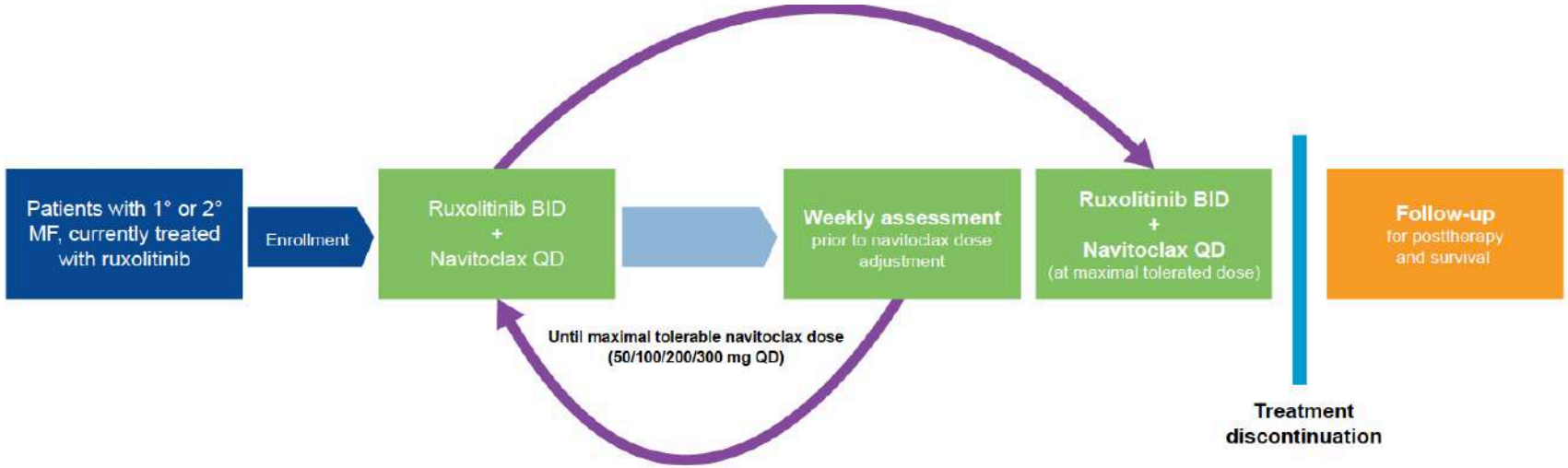
# Navitoclax+ ruxo: proof of concept




- Navitoclax is a potent inhibitor of multiple members of the B-cell lymphoma 2 (BCL-2) family, BCL2, including BCL-$X_L$, BCL-W, which causes cell death by apoptosis
- Navitoclax combined with ruxolitinib may overcome resistance to JAK inhibition
- the synergistic action of JAK2 and BCL-XL/BCL-2 inhibitors induces death in JAK2-mutated cells and BCL-XL inhibition can overcome resistance to JAK2 inhibition
- inhibition of BCL-XL may prevent fibrosis in the bone marrow and navitoclax has been shown to kill activated myofibroblasts

Zeuner et al Blood 2009; 113: 1522-1525; Lagares et al Sci Transl Med 2017:9

# Navitoclax+ ruxo: phase 2 study




- Phase 2 study for primary or secondary MF with palpable spleen> 5 cm who received ruxolitinib for > 12 weeks on a stable dose >10 mg BID for >8 weeks prior to first dose of navitoclax
- Platelet count > 100 x $10^9$/L
- Primary endpoint : SVR at week 24
- 34 patients enrolled

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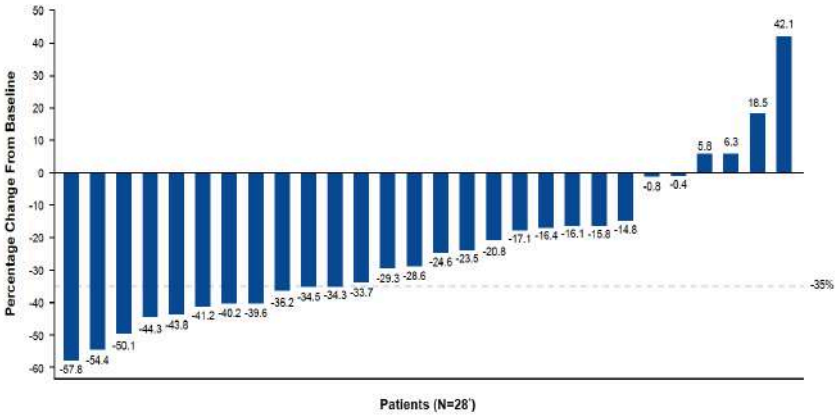
# Navitoclax+ ruxo: efficacy results



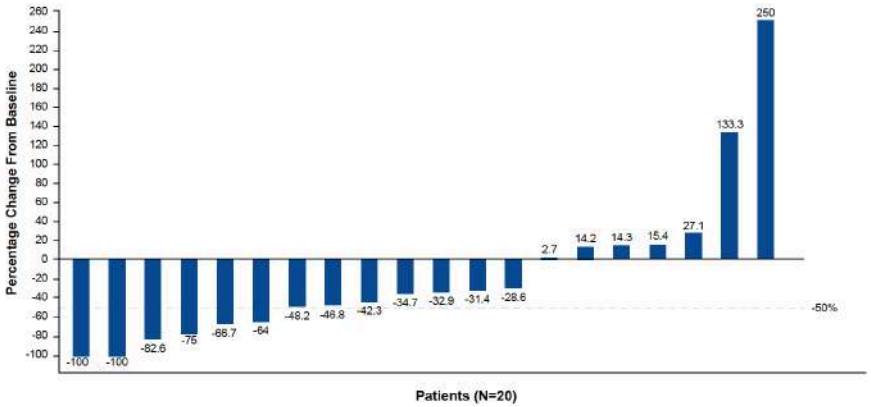

- **SVR ≥35% at week 24** (SVR35) was **27%** (9/34 patients)

– Best on-study SVR35 was 41.2% (14/34 pts)

– Median spleen volume change from baseline was –26.6% (range, –57.8 to 42.1); overall, 18 (52.9%) patients had resolved palpable splenomegaly at week 24

- A reduction in **bone marrow fibrosis of ≥1 grade** was seen in 10 patients (**29.4%**; 95% CI: 15.1, 47.5)

– In total, 4 patients had a 2-grade reduction of fibrosis




- At week 24, 6 patients (**30%**) had a **≥50% reduction from baseline in TSS**, and 13 patients (65%) had any reduction from baseline in TSS

– The median TSS at baseline was 13.7 (range, 0.0 34.5), and at week 24 the median was 6.2 (range, 0.0–24.2)

- Thrombocytopenia was the most common AE (88%), but was reversible and manageable with dose modification. Navitoclax did not adversely impact haemoglobin levels that remained stable over time

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# Conclusions

- The criteria of failure is not yet defined
- Patients in treatment with JAK2i should be carefully monitored in order to optimize the treatment in case of suboptimal responses
- JAK2 inhibitors cannot persistently modify the underlying disease
- Combination strategies seems to attempt to reach different endpoints
- The perfect combination is still not yet realized