

The nightmare of losing response to ruxolitinib in primary myelofibrosis: who can save me?

Gonzalo Carreño Gómez-Tarragona, MD, PhD.

Hematology and Hemotherapy Department

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- Speaker: Novartis, Incyte, Astellas, BMS, GSK, MSD, Pfizer.
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- Research: MSD, Novartis.
- Travel: Janssen.

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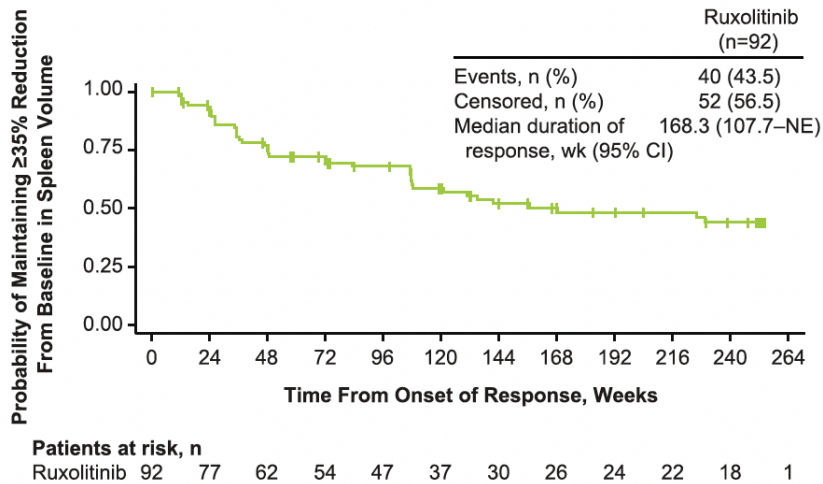
1. When does my patient need a change of treatment? Definition of failure to ruxolitinib.
2. Treatment optimization.
3. New JAK inhibitors: ACVR1 inhibition to the rescue!
4. New drugs and combinations: towards disease modification.
5. MF treatment algorithm in 2025.
6. Conclusions

When does my patient need a change of treatment? Definition of failure to ruxolitinib.

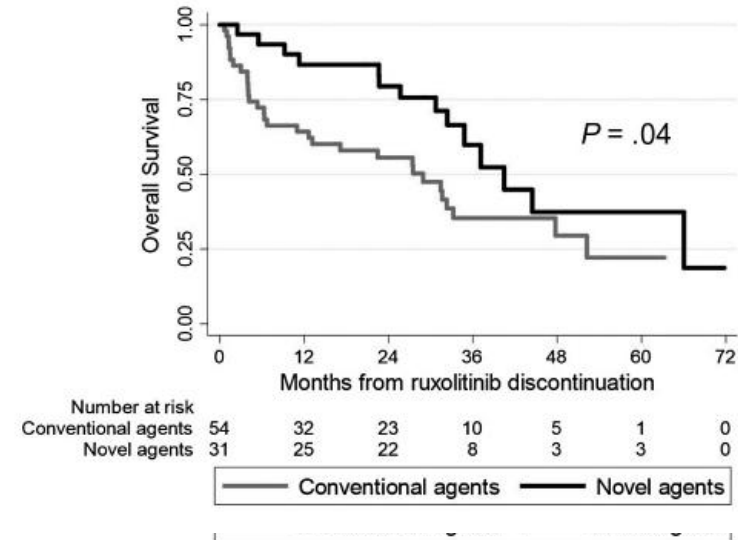
Ruxolitinib failure definition

| Pattern of JAK Inhibitor Therapy Failure | Definition |
|--|--|
| Suboptimal spleen response | <25% reduction in palpable spleen length after at least 3 months of optimally dosed JAK inhibitor therapy |
| Loss of spleen response | ≥50% increase in spleen length from best response |
| Transfusion-dependent anemia | ≥4 units of RBC transfusions in 8 weeks occurring ≥ 6 months from ruxolitinib treatment |
| Severe thrombocytopenia | Unable to maintain unsupported platelet count >35-50x10 ⁹ /L in patients receiving anticoagulation medication; and >25x10 ⁹ /L in patients without anticoagulation |
| Transformation to AP/BP | |
| Second cancers | |
| Infectious complications | |
| Suboptimal symptom response | <50% TSS reduction after at least 3 months of optimally dosed JAK inhibitor therapy |
| Loss of symptomatic response | ≥50% increase of TSS from best response |

The nightmare of ruxolitinib failure

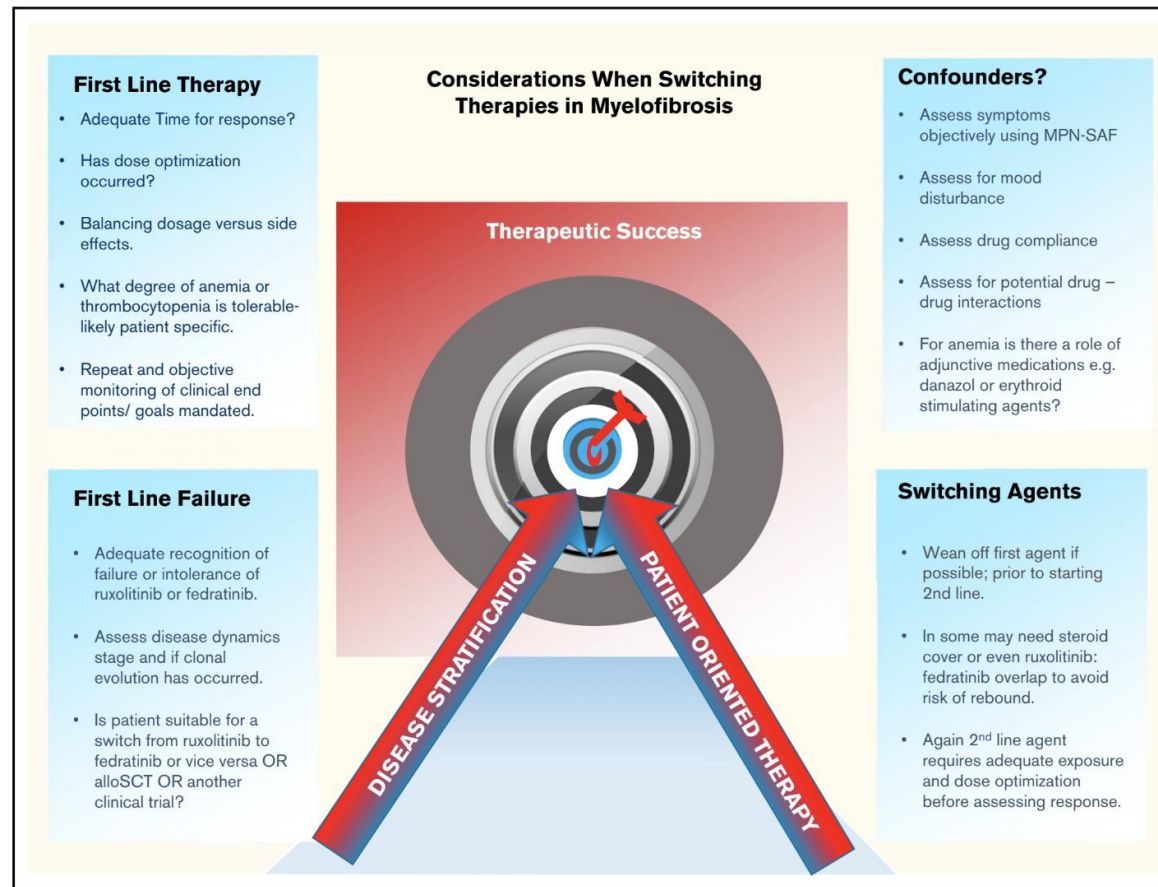


Median duration of reponse to ruxolitinib is 3 years.



Median survival after failure is 13.2 months (27.2 for those in chronic phase and better if the subsequently receive experimental drug)

A complex decision



Treatment Optimization

Am I sure I can't do anything?

| Pattern of JAK Inhibitor Therapy Failure | Optimization Strategy for Ruxolitinib |
|--|---|
| Suboptimal spleen response | Increase JAK inhibitor dose depending on Hb and platelet counts |
| Loss of spleen response | Increase JAK inhibitor dose depending on Hb and platelet counts |
| Transfusion-dependent anemia | Decrease JAK inhibitor dose |
| Severe thrombocytopenia | Decrease JAK inhibitor dose |
| Transformation to AP/BP | Continue JAK inhibitor therapy if required for splenomegaly and symptoms, dose adjustment depending on Hb and platelet counts |
| Second cancers | Case-by-case discussion of JAK inhibitor therapy discontinuation |
| Infectious complications | Consider if there would be benefit from adding prophylactic strategies to prevent recurrent infections |
| Suboptimal symptom response | Increase JAK inhibitor dose depending on Hb and platelet counts |
| Loss of symptomatic response | Increase JAK inhibitor dose depending on Hb and platelet counts |

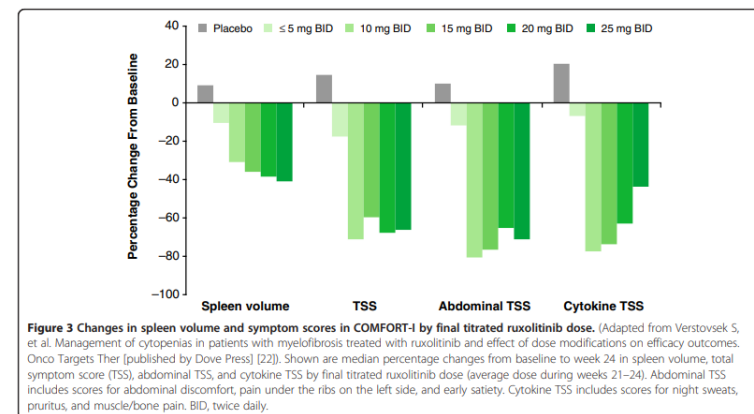
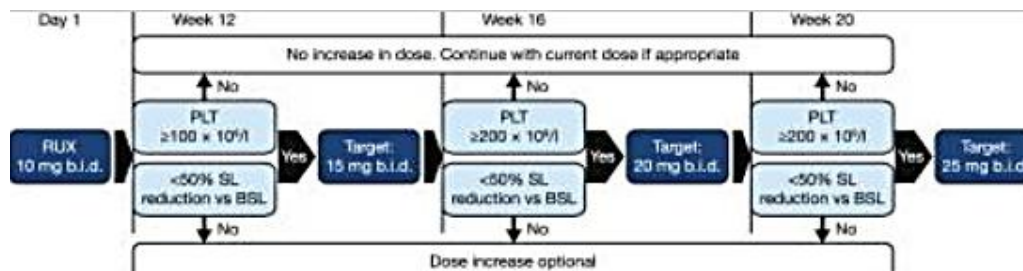
Optimization Strategies

ESA

| Prior transfusion support | | | | |
|---------------------------|-----|-----|------------------|------|
| Yes, with dependency | 24 | 29% | Baseline | .026 |
| Yes, without dependency | 39 | 49% | 2.31 (0.78-6.80) | .13 |
| No | 100 | 60% | 3.64 (1.39-9.58) | .009 |

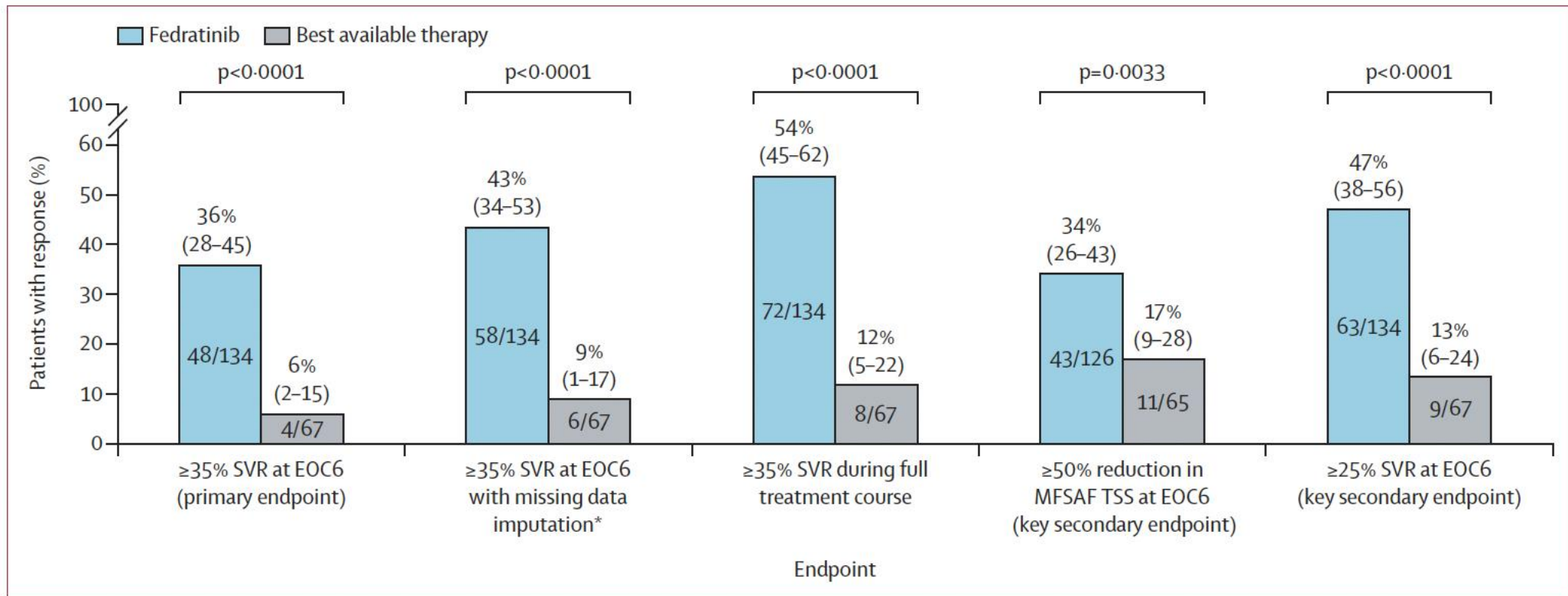
53% responses, median duration 19 months

Ruxo dosing

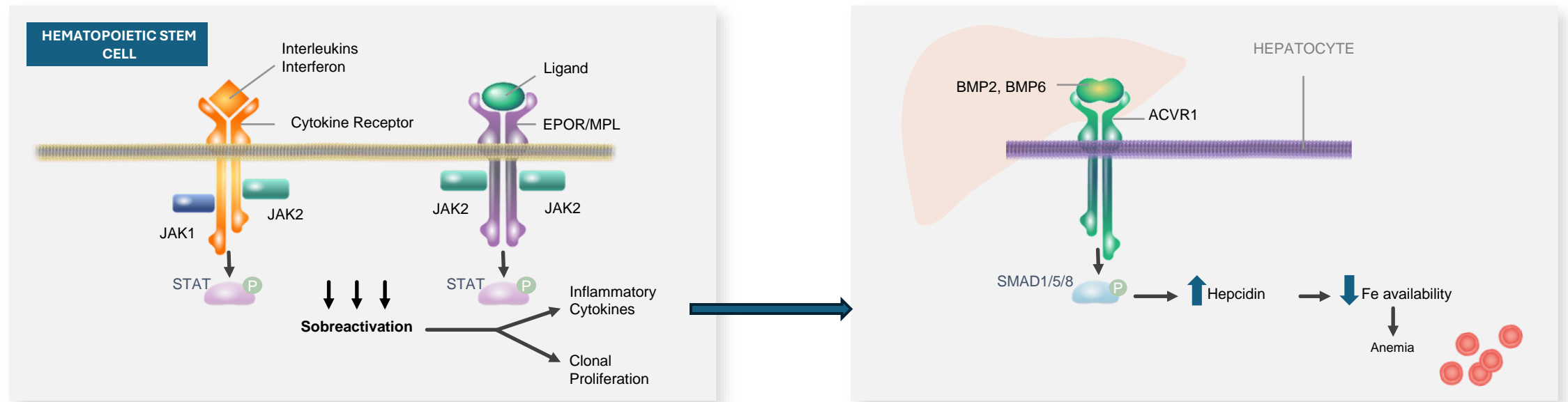


New JAK inhibitors: ACVR1 inhibition to the rescue!

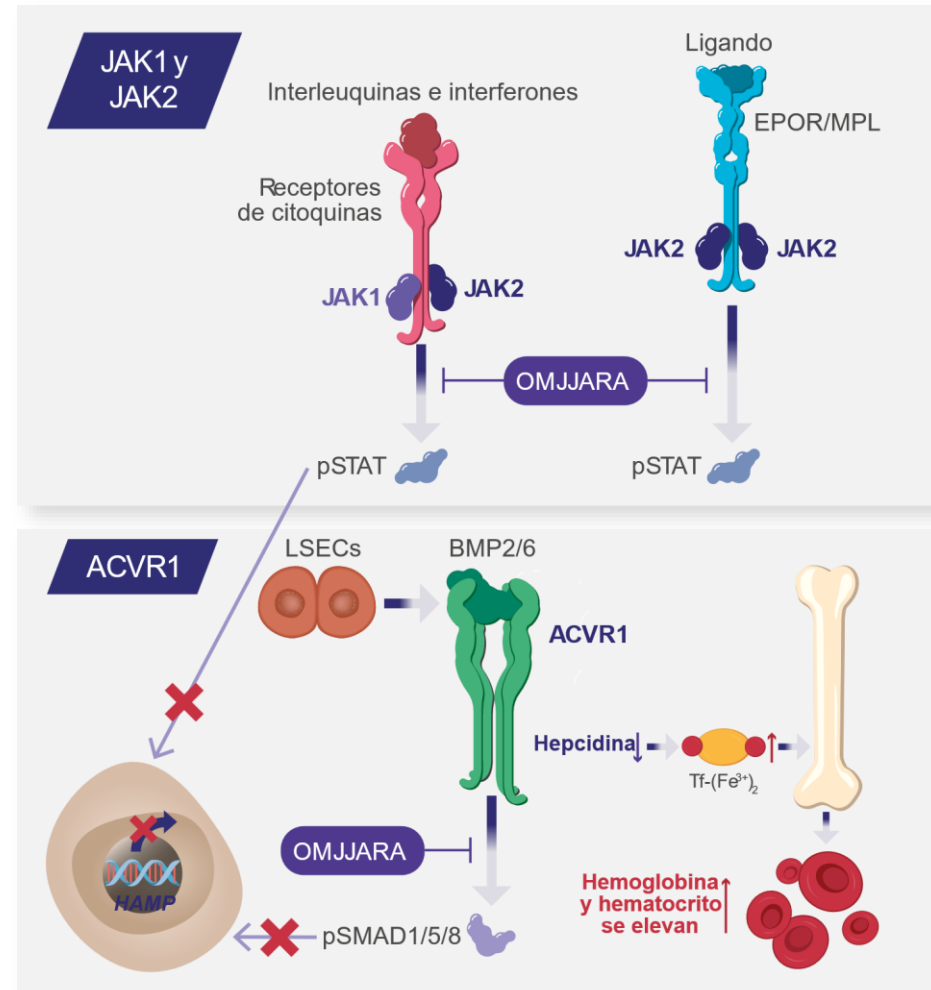
Fedratinib



Momelotinib: a game changer

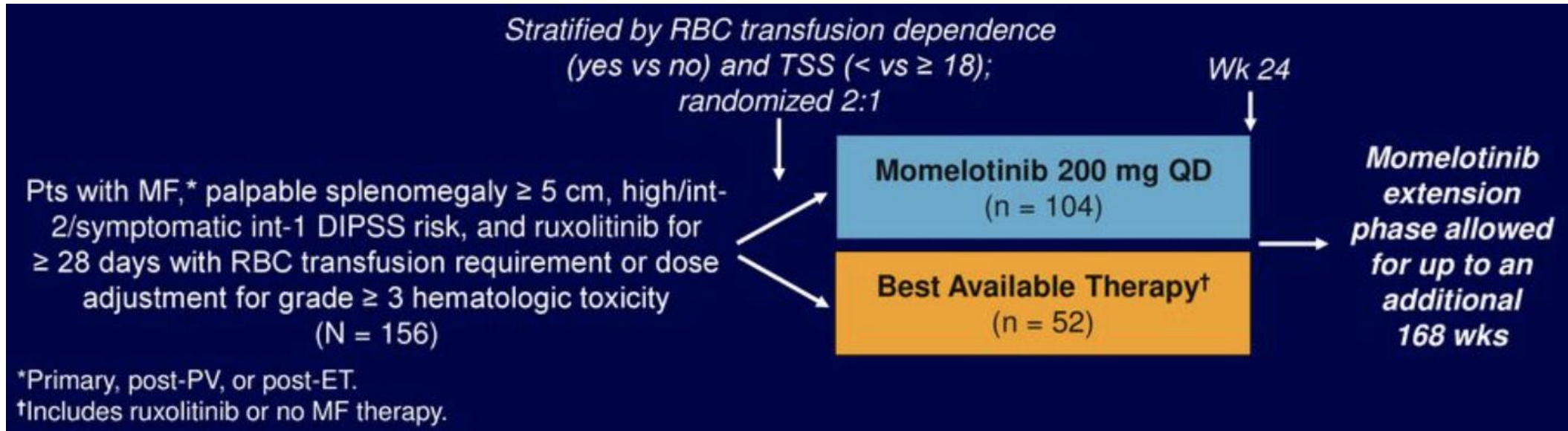


Momelotinib: a game changer



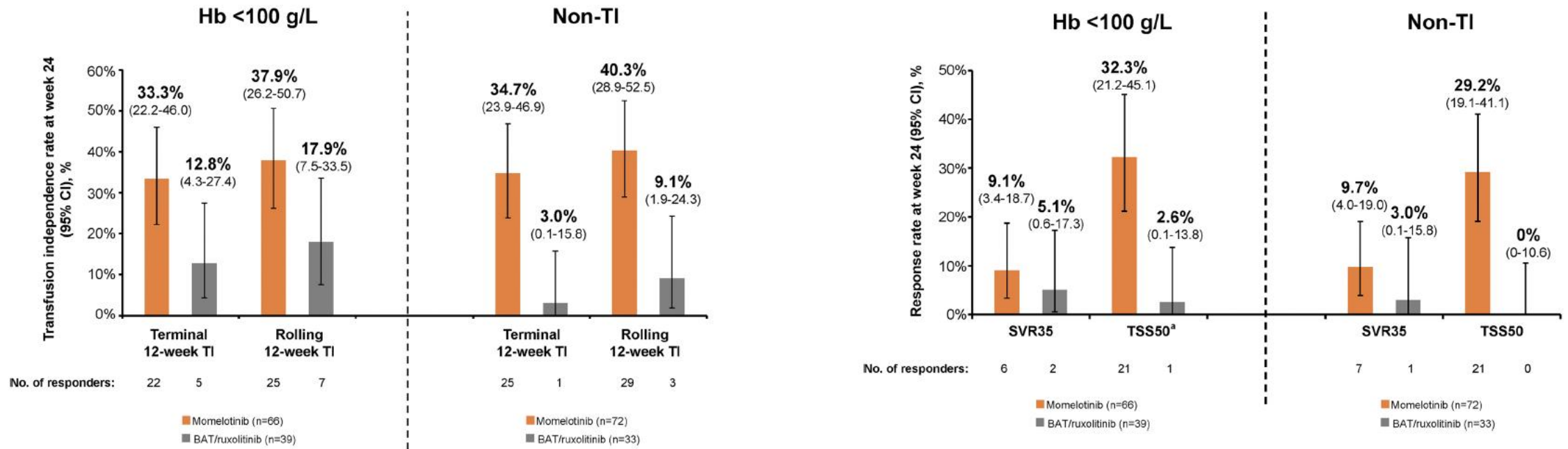
Momelotinib: a game changer

Simplify-2



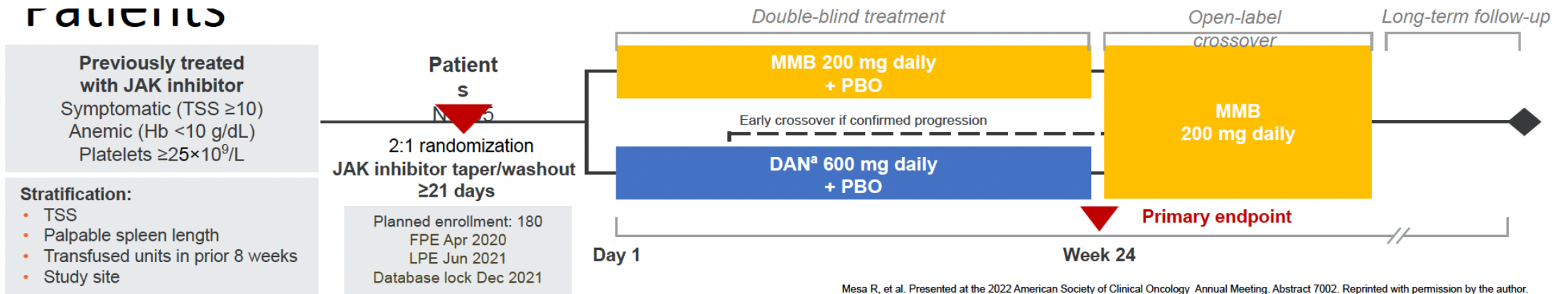
The primary endpoint (superiority) was splenic response rate (spleen volume reduction ≥ 35% from baseline) at week 24. Secondary endpoints included TSS response rate (≥ 50% reduction from baseline) and transfusion independence rate (no RBC transfusions or Hb of < 80 g/L in the last 12 weeks before week 24). TSS was assessed in patients with baseline TSS of > 0 or baseline TSS of 0 but missing or > 0 at week 24. In addition to the prespecified terminal

Momelotinib: a game changer



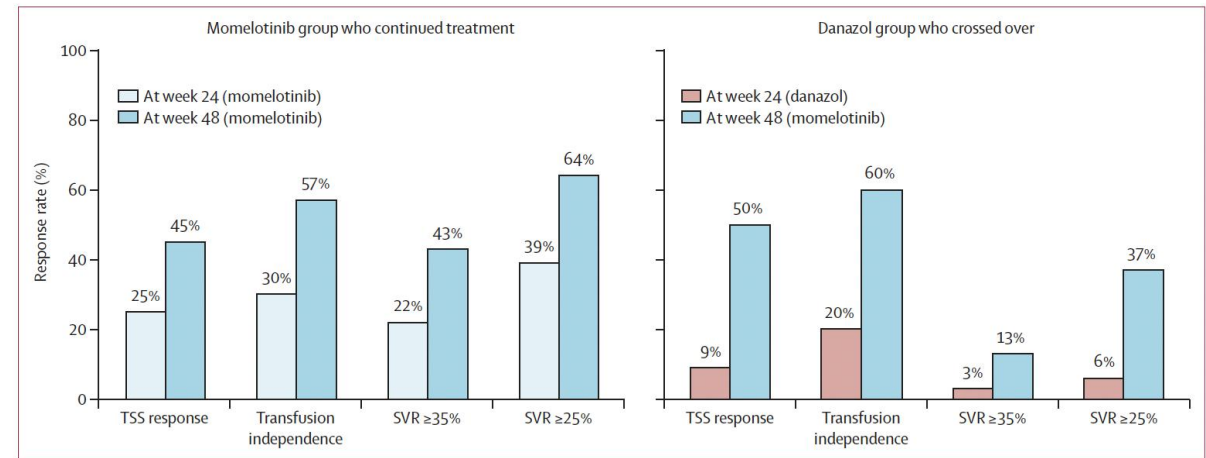
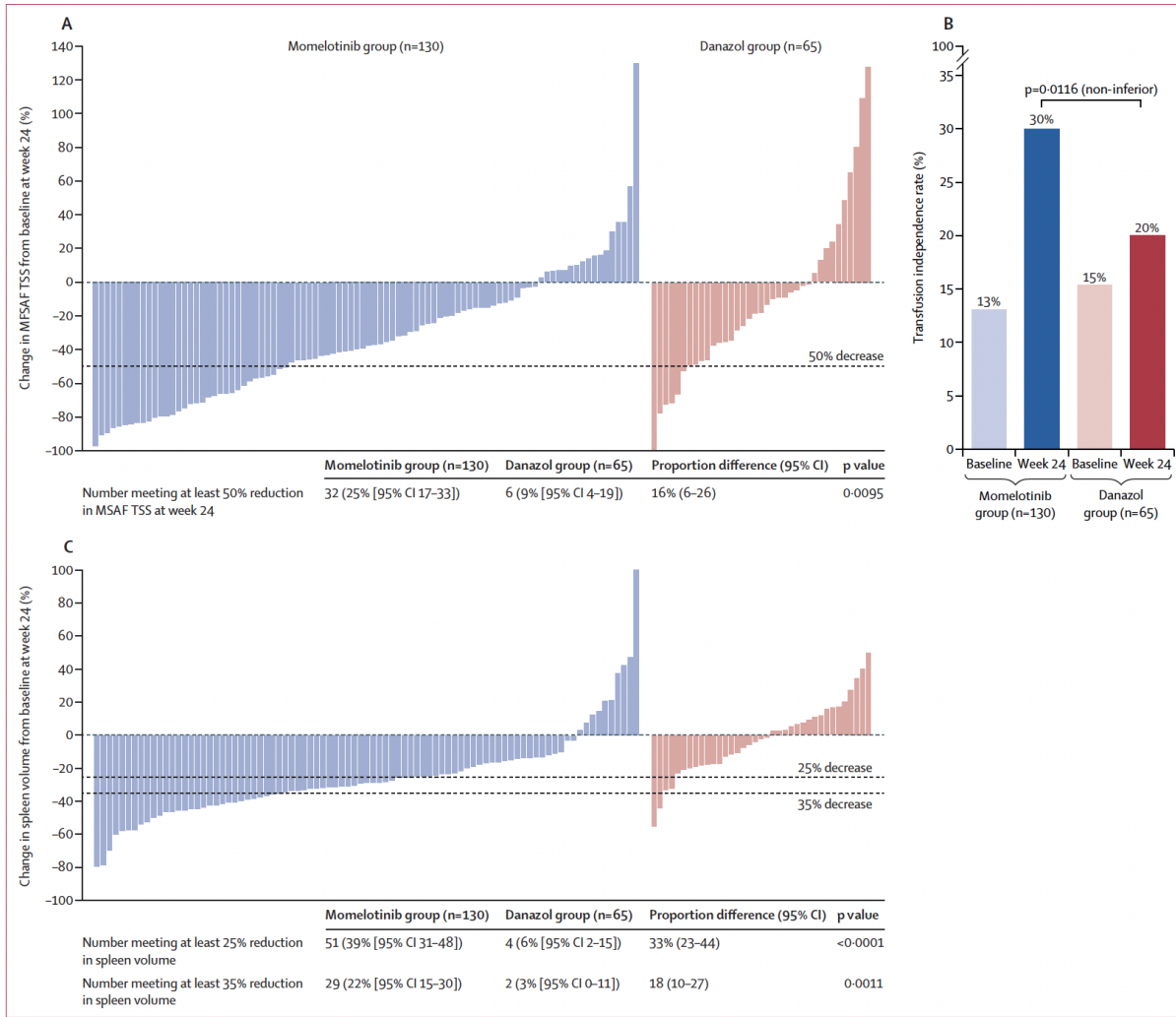
Momelotinib: a game changer

MOMENTUM



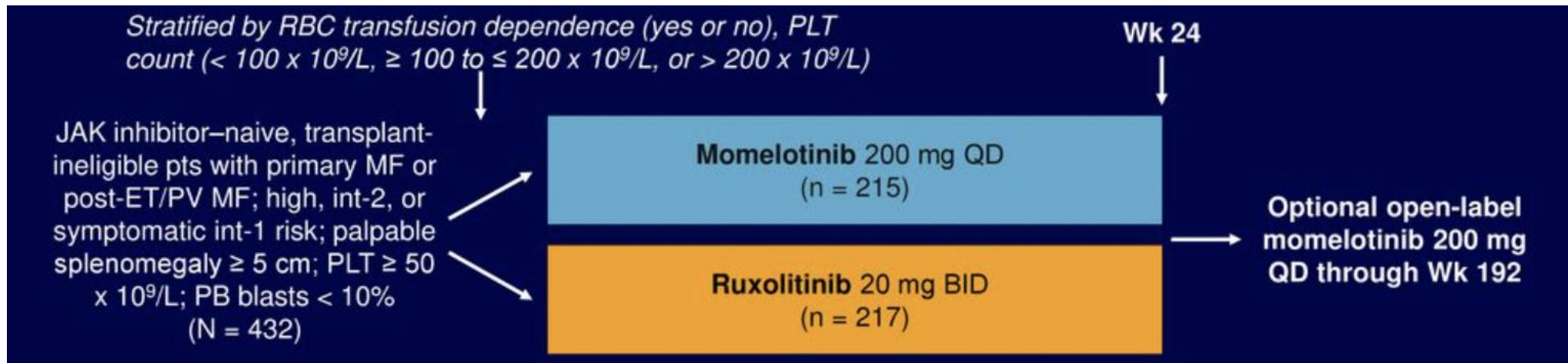
The primary endpoint was MFSAF TSS response rate at week 24, defined as the proportion of patients with a 50% or more reduction in mean MFSAF TSS over the 28 days immediately before the end of week 24 compared with baseline. Key secondary endpoints included in the 50% or more reduction in mean MFSAF TSS over the 28 days immediately before the end of week 24 compared with baseline. Key secondary endpoints included in the

Momelotinib: a game changer



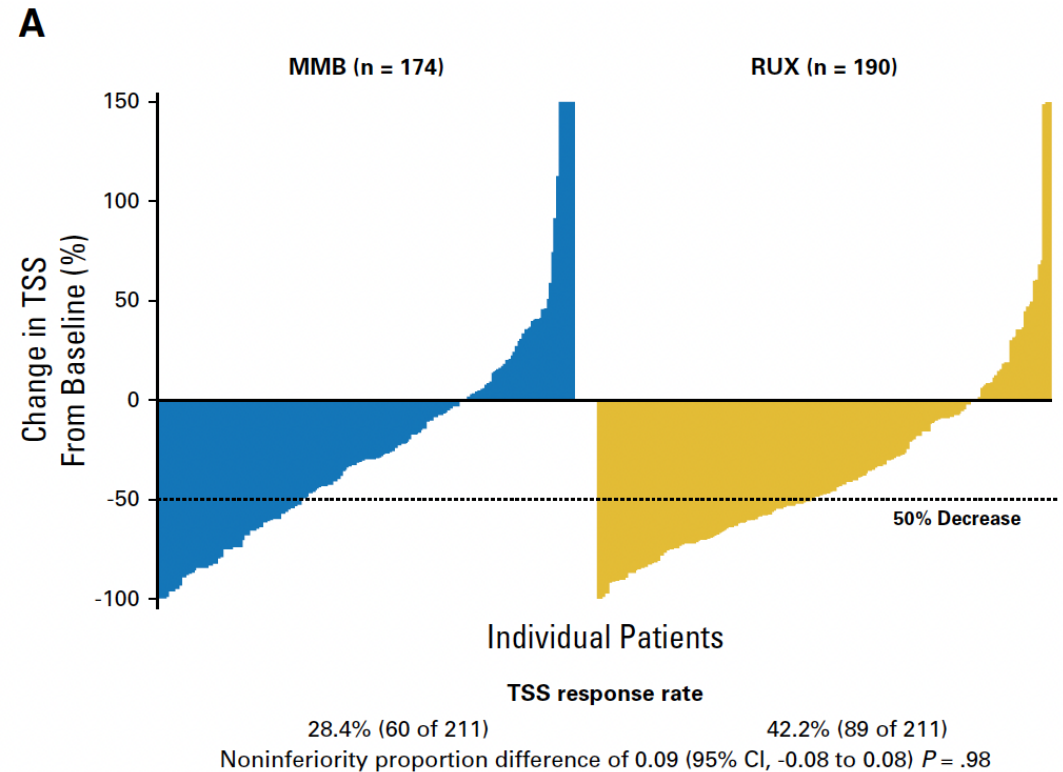
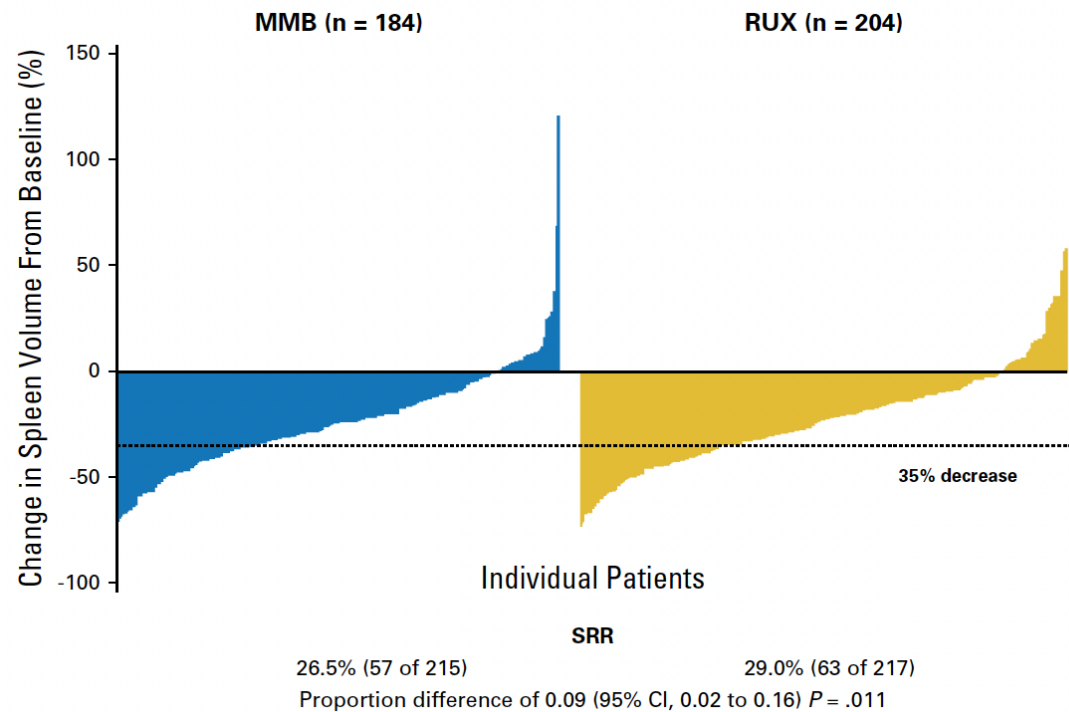
Momelotinib: a game changer also in first line

Simplify-1

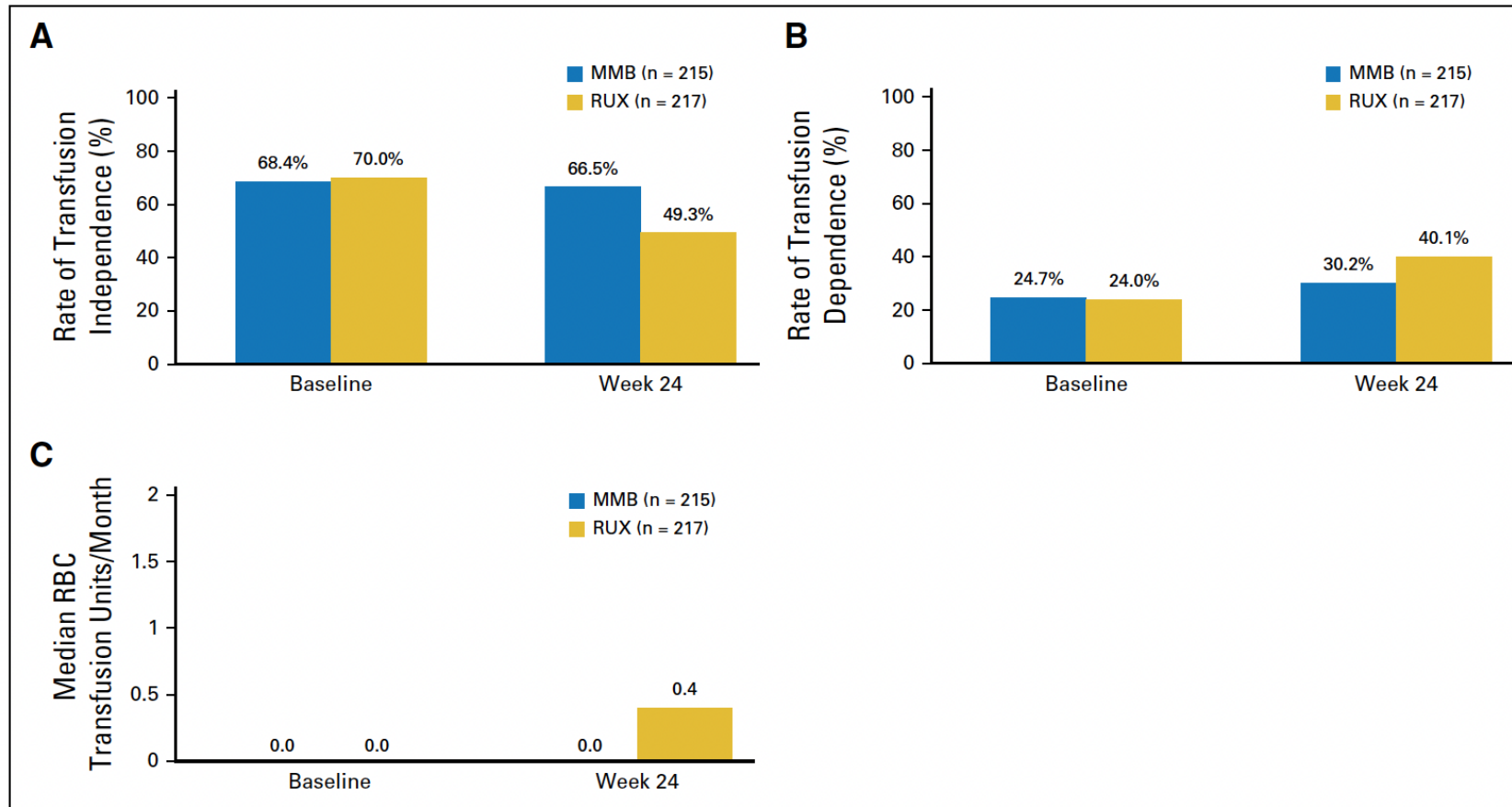


The primary end point was a reduction of $\geq 35\%$ in spleen volume from baseline at week 24 (spleen response rate, SRR24), as assessed by MRI or CT scan and evaluated by a blinded central reader. The primary hypothesis was that momelotinib is noninferior to ruxolitinib. On the basis of

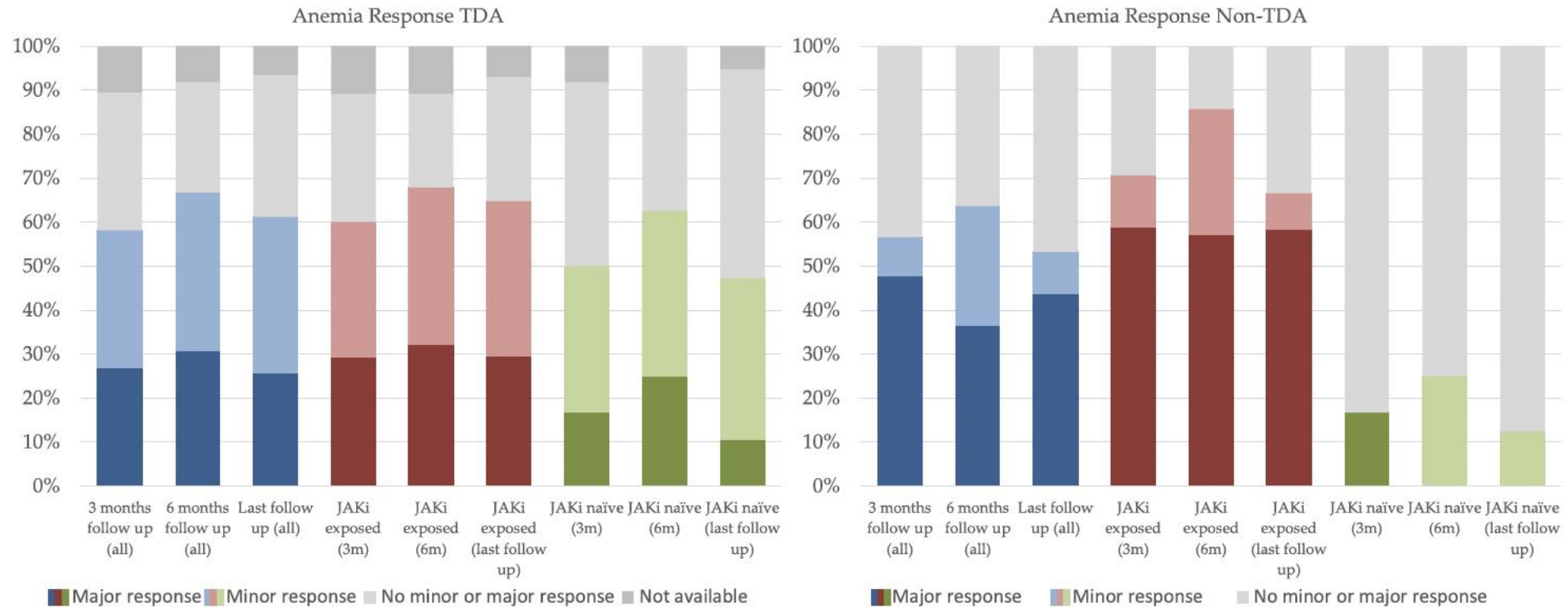
Momelotinib: a game changer also in first line



Momelotinib: a game changer also in first line

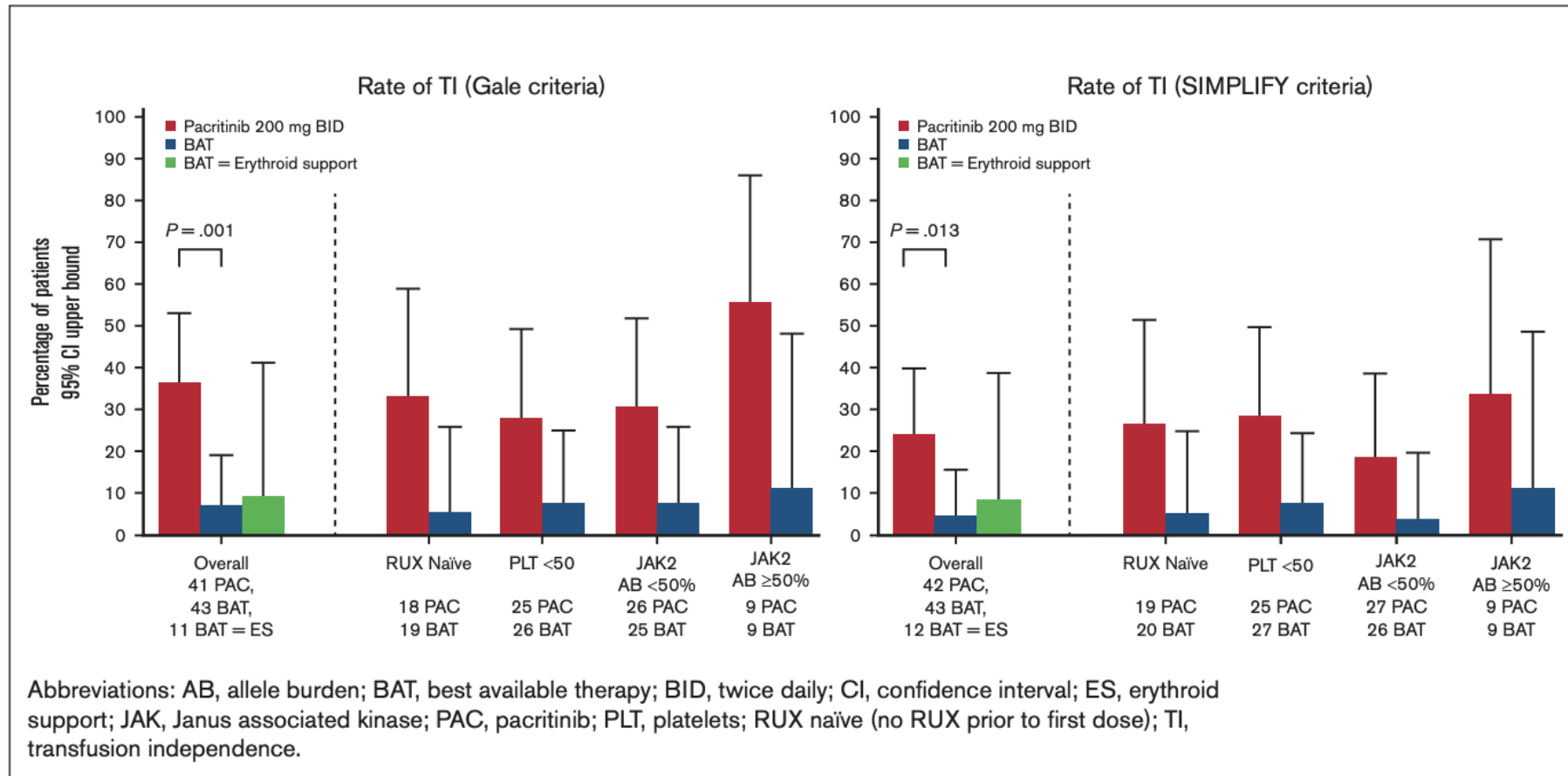


Momelotinib: the Spanish experience

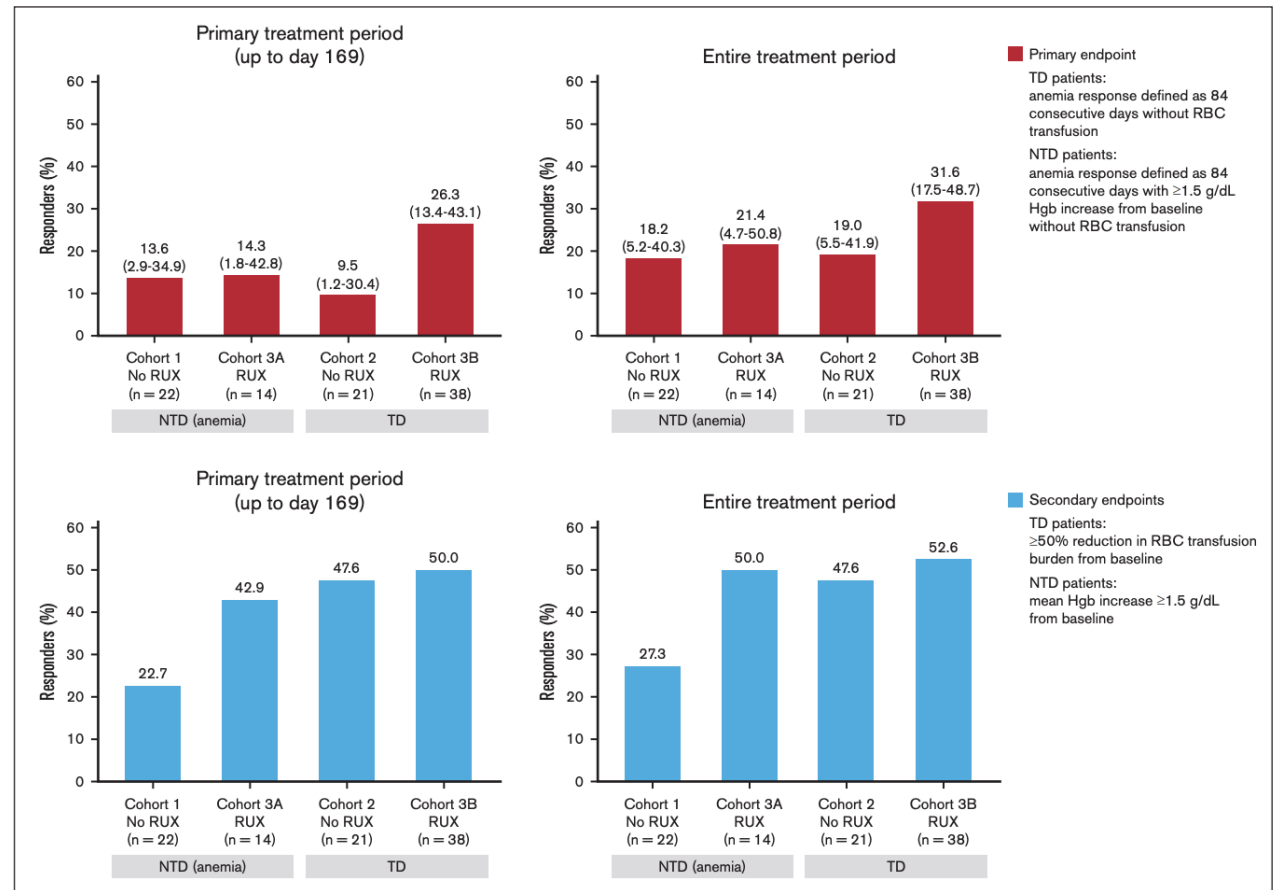
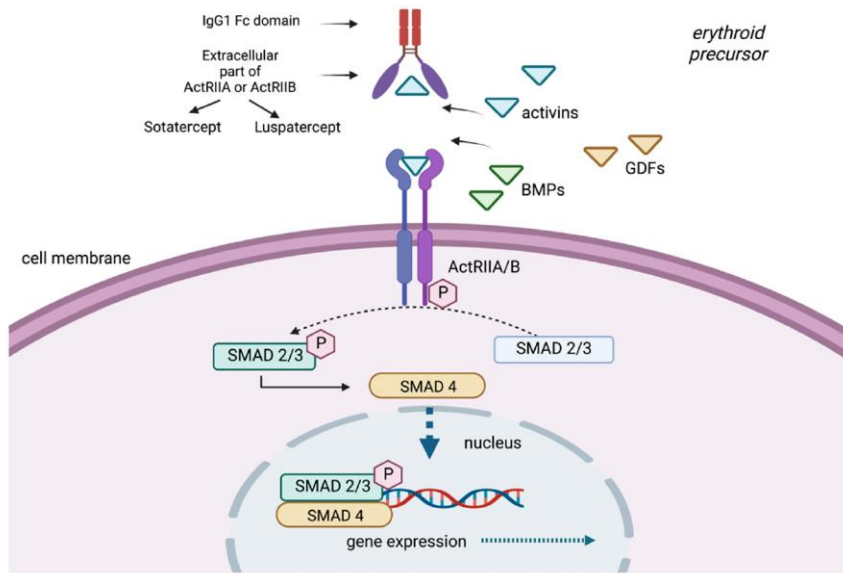


124 patients (23.4% naïve, median Hb 8g/dl,
70% transfusion dependent)

Pacritinib



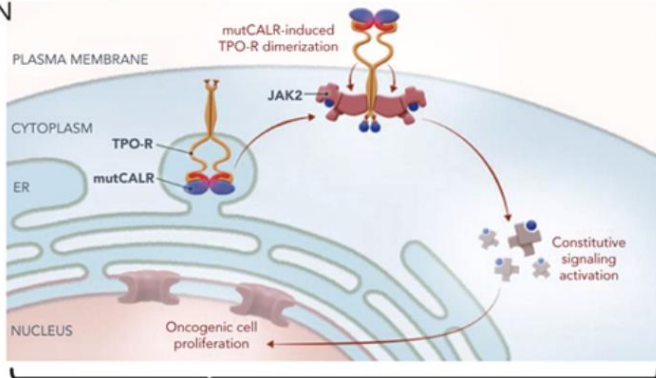
Other ACVR1 inhibitors



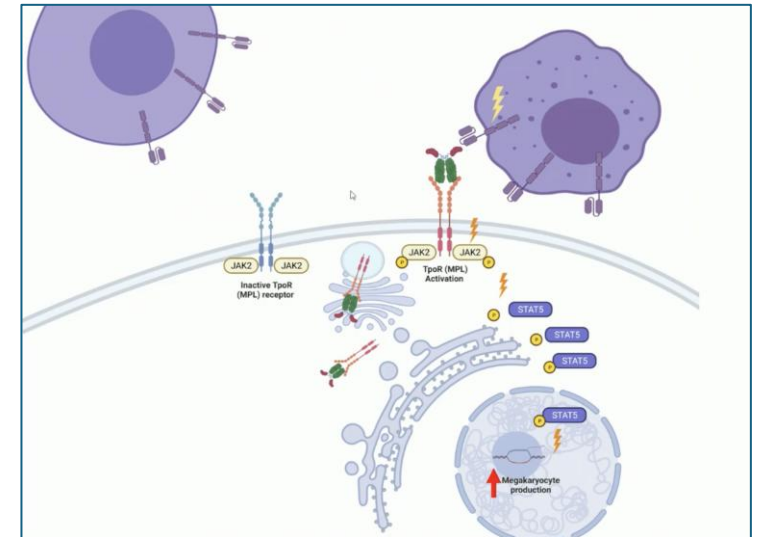
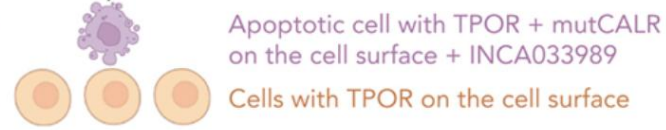
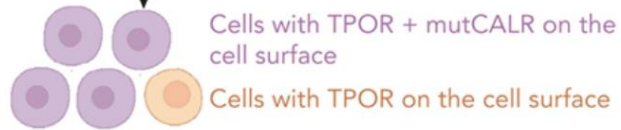
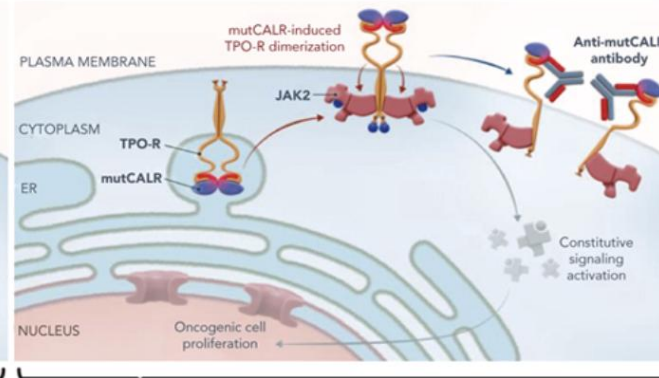
New drugs and combinations: towards disease modification.

Immunotherapy is coming

Mutant calreticulin (mutCALR) binds TPO-R and induces oncogenic cell proliferation in CALR-mutant MPN

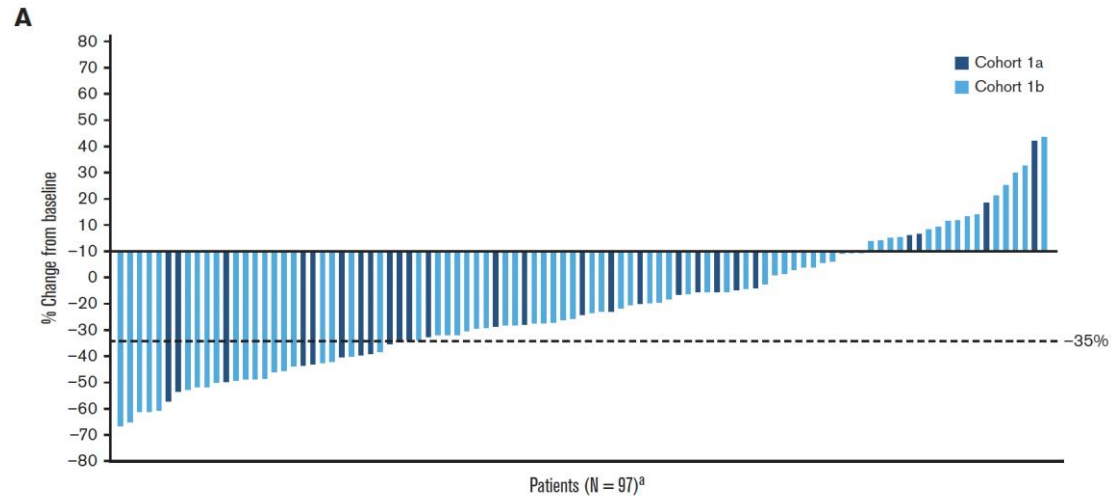


INCA033989 prevents TPO-R activation and selectively inhibits oncogenic cell proliferation



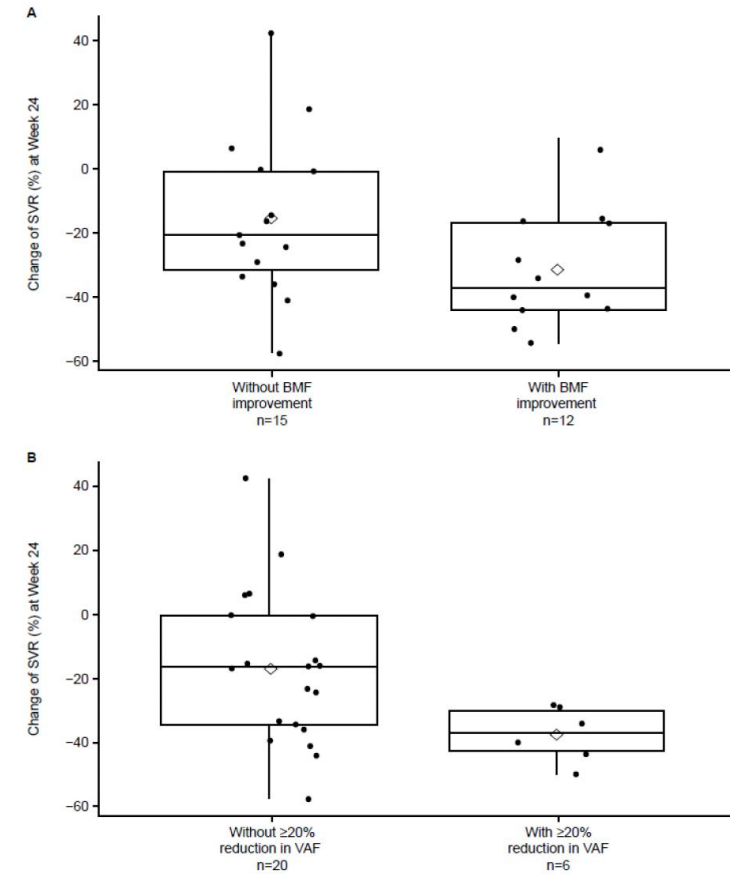
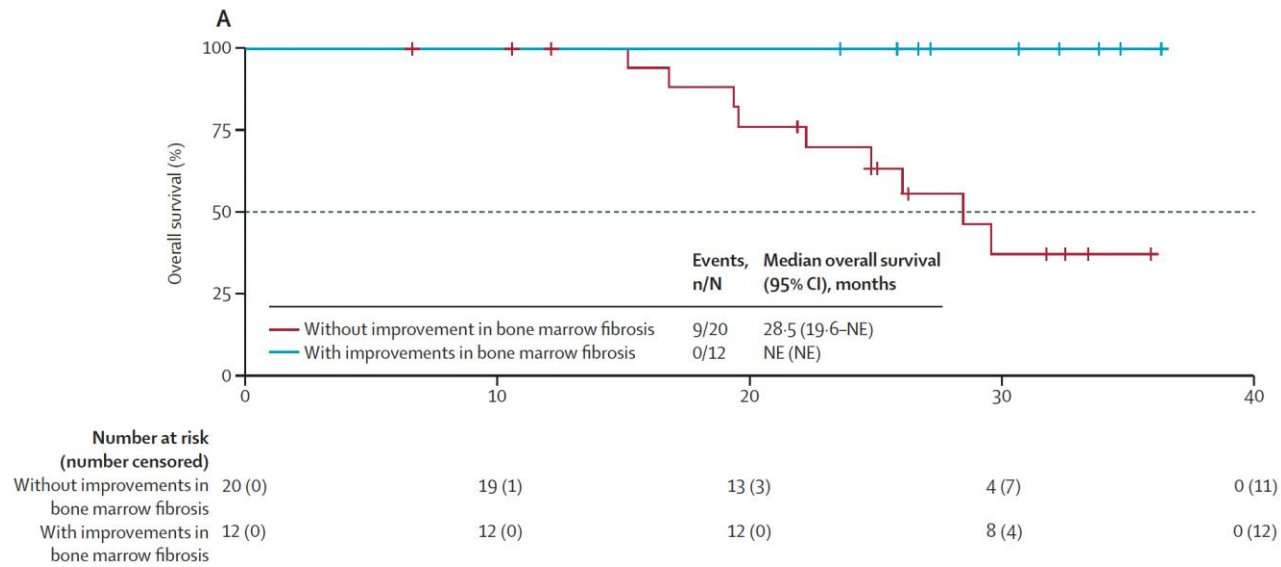
Also combination therapy... but it is not easy!

An example: Navitoclax+Ruxolitinib



200 mg/d if platelet count was ≤ 150 or $> 150 \times 10^9/L$, respectively. The primary end point was spleen volume reduction of $\geq 35\%$ (SVR₃₅) at week 24. Secondary end points included $\geq 50\%$ total symptoms score (TSS₅₀) reduction at week 24, bone marrow fibrosis (BMF) grade changes, anemia response, and safety. In total, 125 patients received ≥ 1 dose of NAV+RUX. With median follow-up of 21 months, SVR₃₅ rate was 23% at week 24 and 39% at any time on study (median duration: 11 months). TSS₅₀ rate was 24% at week 24 and 46% at any time on study. BMF improved by ≥ 1 grade, any time on study, in 39% of patients. Anemia responses were achieved in 23% of patients. Median overall and progression-free survival were 52.3 and 22.1 months, respectively. No new safety signals were observed. The most common adverse event was thrombocytopenia without clinically significant bleeding. NAV+RUX was tolerable and demonstrated early improvement in disease modification parameters in this difficult-to-treat population. This trial was registered at www.ClinicalTrials.gov as #NCT03222609.

Can we modify the disease biology?



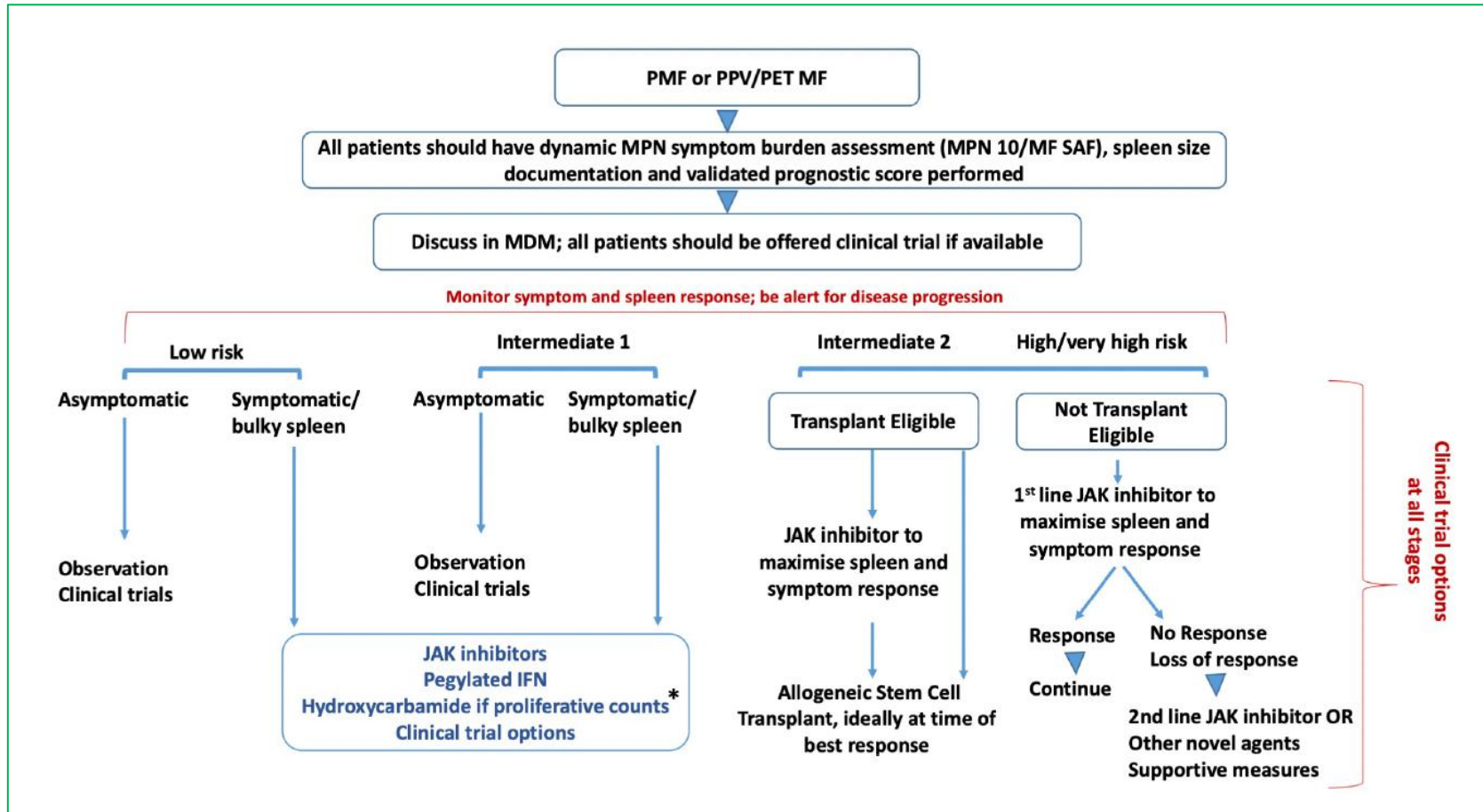
What is disease modification?

Disease modification in MF is defined as therapy that exerts a clinically meaningful impact on survival outcomes and/or restoration of normal hematopoiesis in conjunction with improvement in bone marrow fibrosis through a substantial and durable reduction in the clonal burden of disease.

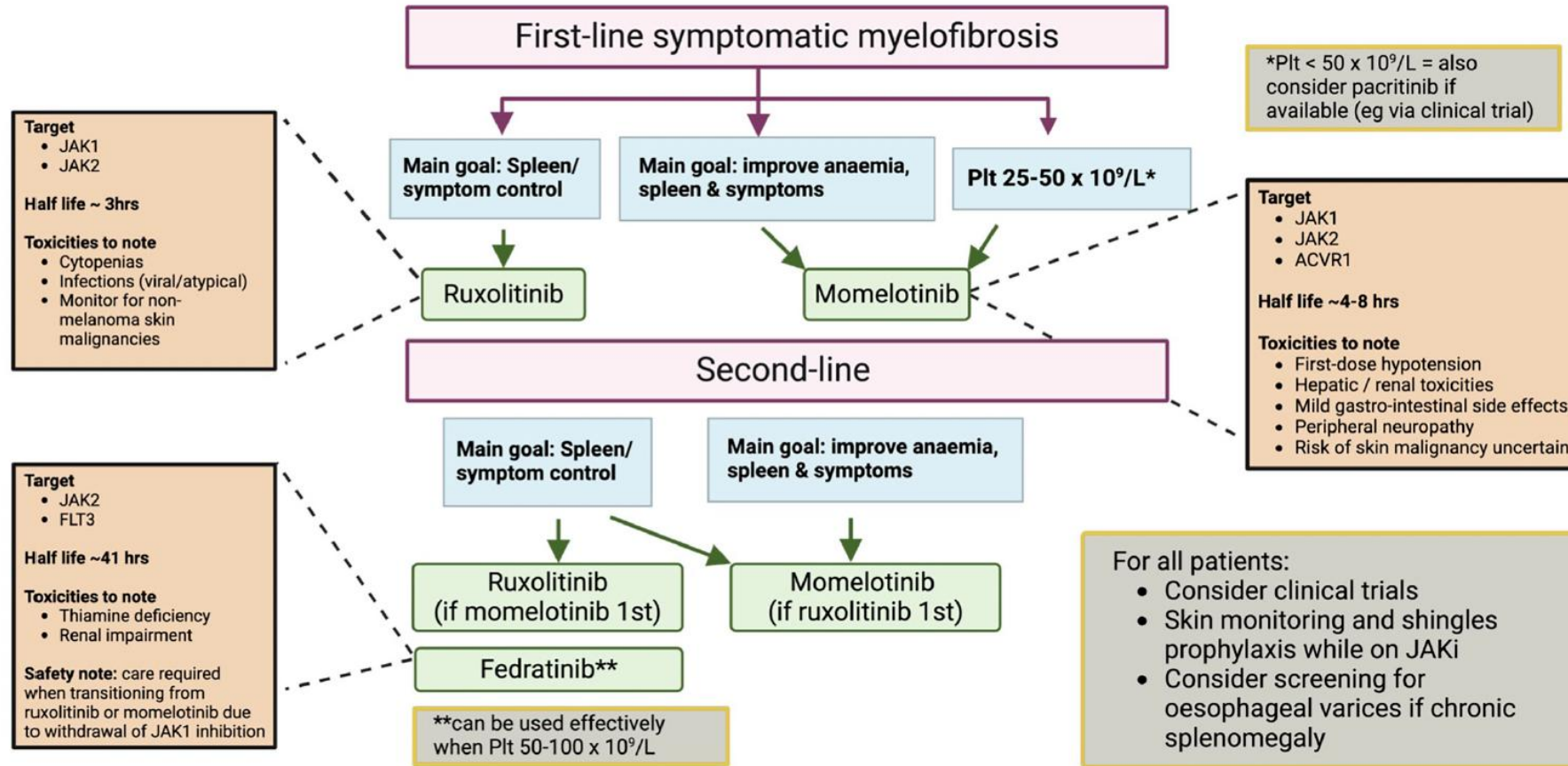
We need more data!

MF treatment algorithm in 2025.

MF Treatment Overview



Which JAKi do I choose?



Conclusions

Conclusions

1. Half of MF patients will lose response to ruxolitinib after 3 years.
2. Prognosis is dismal after ruxolitinib failure.
3. Ruxolitinib treatment can be optimized (dose, ESA...).
4. New JAK inhibitors (or trials!) are the best option after ruxolitinib.
5. Momelotinib's ACVR1 inhibition makes it the best option for cytopenic patients (and not only in the second line!)
6. New drugs are coming that hopefully will change MF's biology and improve our patient's survival and quality of life.

Thank you!



@GonzaloHEM
gonzalo.carreno@salud.madrid.org