What is disease modification in myelofibrosis?

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Disclosures

Name of Company	Research support (clinical trials)	Consultant/ Scientific Advisory Board	Honoraria	Travel reimbursement
Blueprint	x	x	x	x
Novartis	x	x	x	x
BMS	x	x	x	x
AOP	x	x	x	x
GSK	x	x	x	x
Abbvie	x	x	x	x
Incyte	x	x		
Cogent	x	x		
Astra Zeneca	x			

Disease modification in myelofibrosis

- 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**.
- To prevent progression, we must **deplete MPN stem cells** and **disarm the tumor-promoting microenvironment**, which will require the use of strategies utilizing approaches that **target pathwavs beyond JAK/STAT signaling**. JAK2 inhibitors are **NOT** the only target for effective drug development.

Pemmaraju et al., Cancer 2022; Hofmann R., expert commentary

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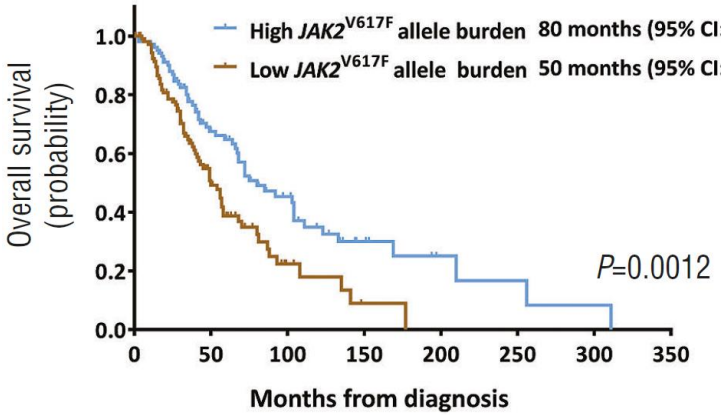
Reticulin and collagen fibrosis, osteoscelerosis

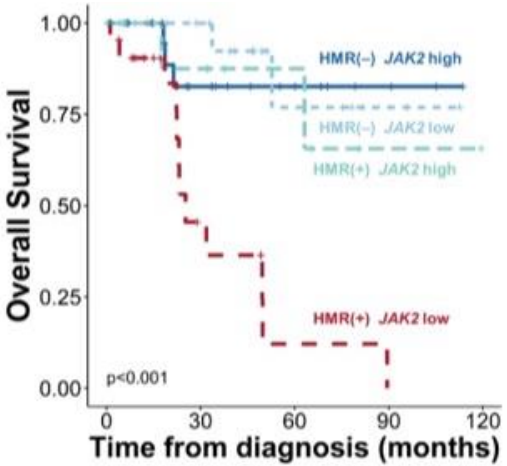
Multifactorial reasons for cytopenias, beside fibrosis, e.g. dysplasia, inflammation, splenomegaly, toxicity

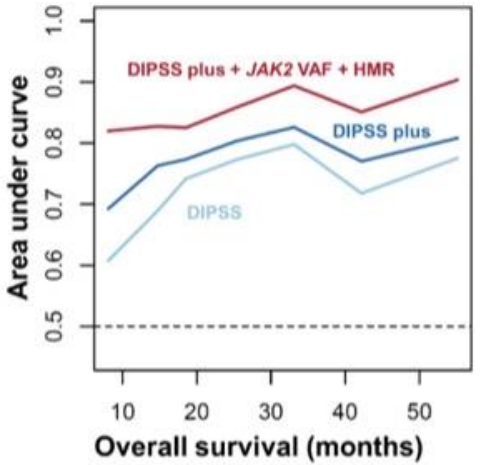
Complex genetics

Pemmaraju et al., Cancer 2022; Hofmann R., expert commentary

HMR Mutations Drive Poor Prognosis in Myelofibrosis Patients with Lower JAK2V617F Allele Burden but Not in Those with Higher Allele Burden: Results of a Multicenter Study

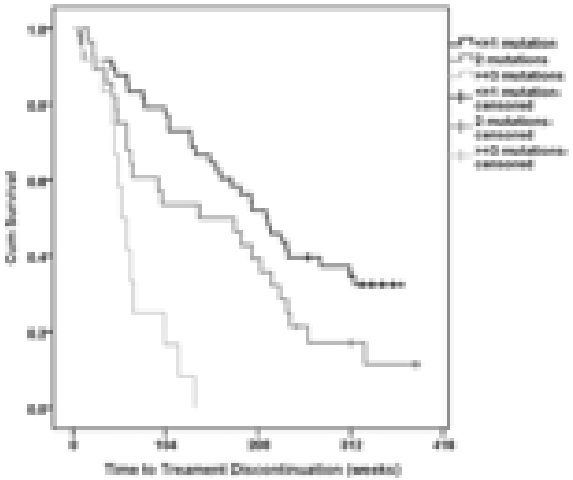


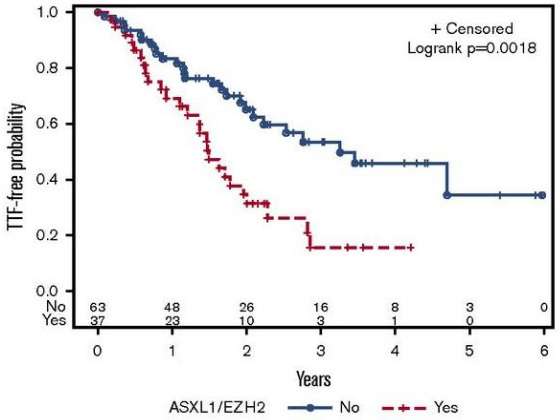


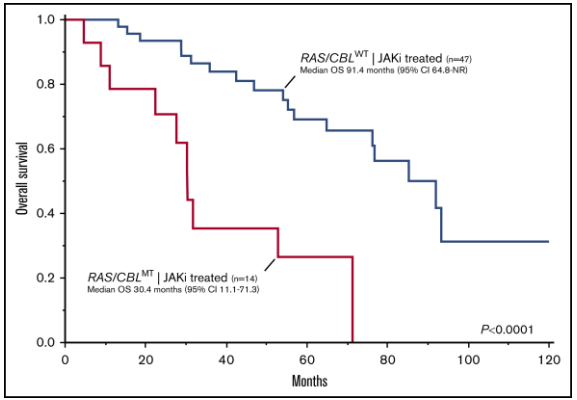


Wang et al., Abstract #627, ASH 2023

Impact of genomics on response to Jak inhibitor therapy







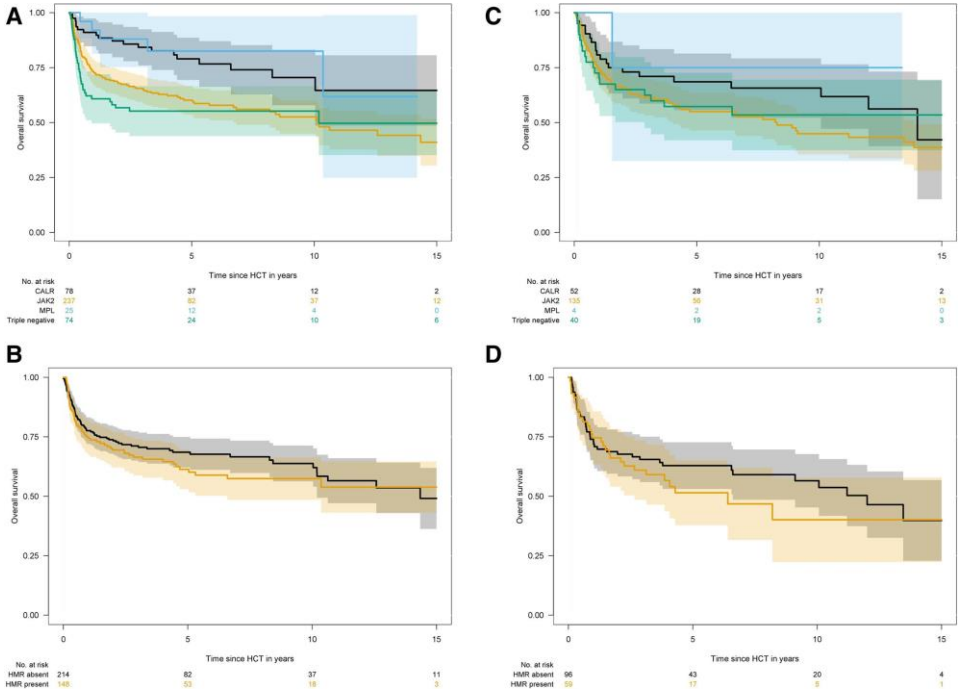
Patel et al., Blood 2015; Spiegel et al., Blood Adv. 2017; Coltro et al., Blood Adv. 2020

Disease modification in myelofibrosis

Parameters	Rationale	Supporting Data From Novel Agents	Limitations
Primary outcomes of disease modification			
Overall survival (event-, progression- or leukemia-free survival)	• Most critical outcomes of any life-threatening disease treatment	• **Not generally a primary end point** • **Imetelstat and tagraxofusup reported median OS of 30 and 31 mo, respectively**	• Require lengthy follow-up • may not be compatible with timelines for drug approval
Key modifiers			
Bone marrow fibrosis	• contributes to **splenomegaly** and **cytopenias** • **directly influences OS** • allo-SCT leads to reversal	• **Improvement corelated with OS: Imetelstat** • **Improvement reported by: pelabresib, bomedemstat, navitoclax, navtemadlin**	• Uncertainties on grading and timing • Only significant if associated with improvement of cytopenias
Clonal disease/ mutational burden	• Correlated with **phenotype** and **progression/evolution**	• **Reduction correlated with OS: Imetelstat** • **Reductions reported by: bomedemstat, navitoclax, navtemadlin**	• Uncertainties on importance (driver mutations, additional mutations, clonal hematopoiesis), standardization, grading, timing and association with OS
Inflammatory cytokine signature	• Key modifier of the BM **microenvironment** and promoter of **malignant hematopoiesis**	• **Reductions demonstrated by: pelabresib, navitoclax, navtemadlin**	• Uncertainties upon association with survival outcomes

Modified from Pemmaraju et al., Cancer 2022

High Molecular and Cytogenetic Risk in Myelofibrosis Does Not Benefit From Higher Intensity Conditioning Before Hematopoietic Cell Transplantation: An International Collaborative Analysis



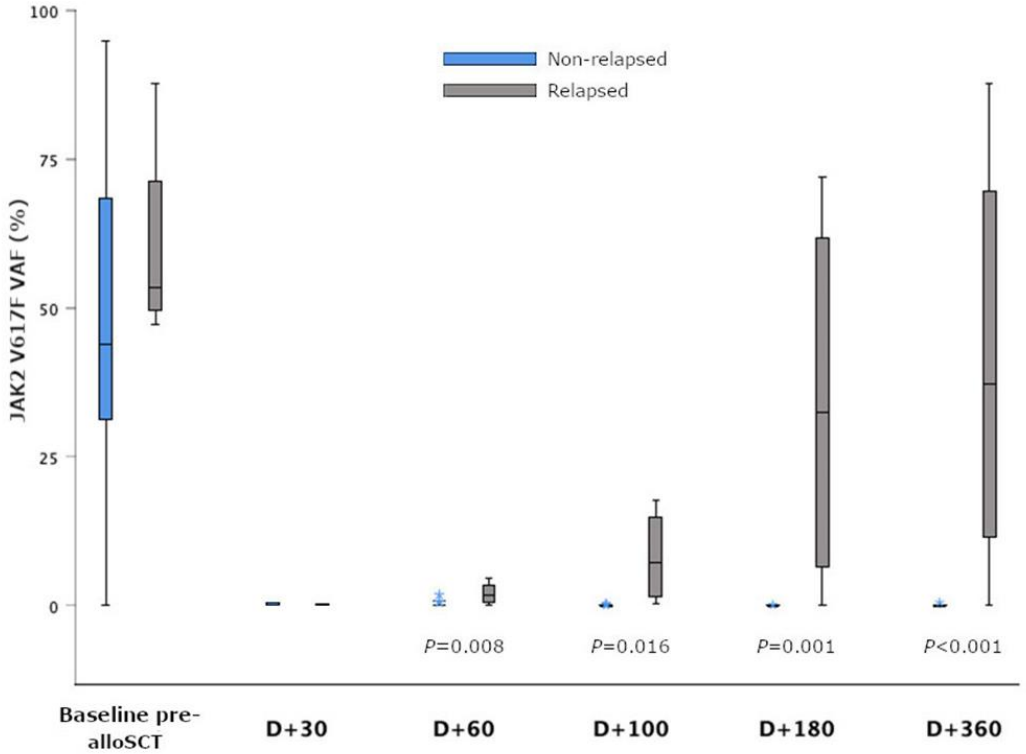
Reduced intensity conditioning

Myeloablative conditioning

Gagelmann et al., HemaSphere 2022

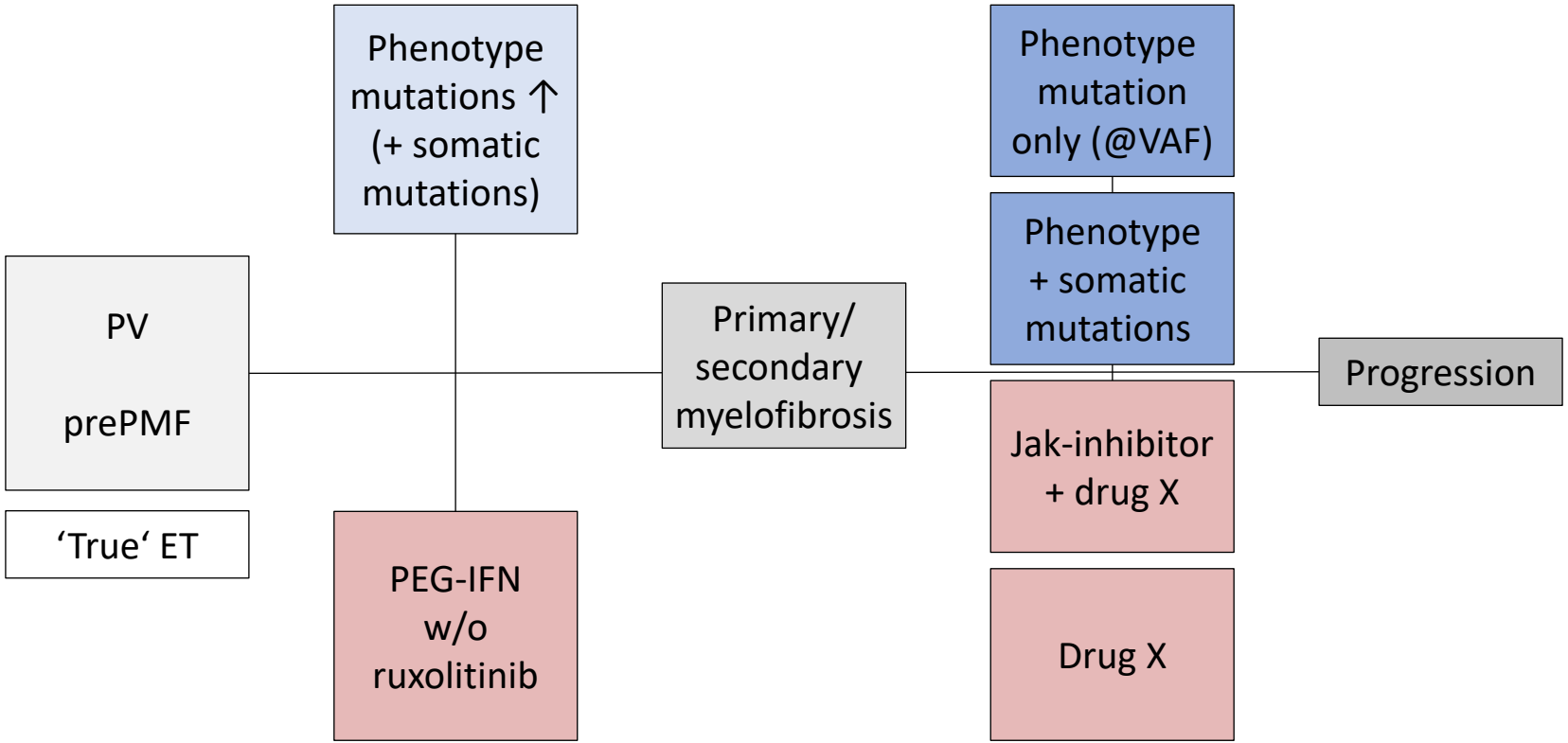
Sensitive Molecular Detection of *JAK2* V617F Is a Predictive Marker of Relapse in Patients with Myelofibrosis after Allogeneic Stem Cell Transplantation

Figure 1. Comparison of *JAK2 V617F* variant allele frequency (VAF) between relapsed and non-relapsed patients at different time points post-allogeneic stem cell transplant (alloSCT)



Nedumannil et al., Abstract #629, ASH 2023

Disease modification in myelofibrosis



Disease modification in advanced systemic mastocytosis

AdvSM

- ASM, SM-AHN, MCL
- *KIT* D816V (>95%)
- Somatic mutations (~60-80%, prognosis!!!)
- Chromosomal abnormalities (~20-30%)
- Multilineage involvement

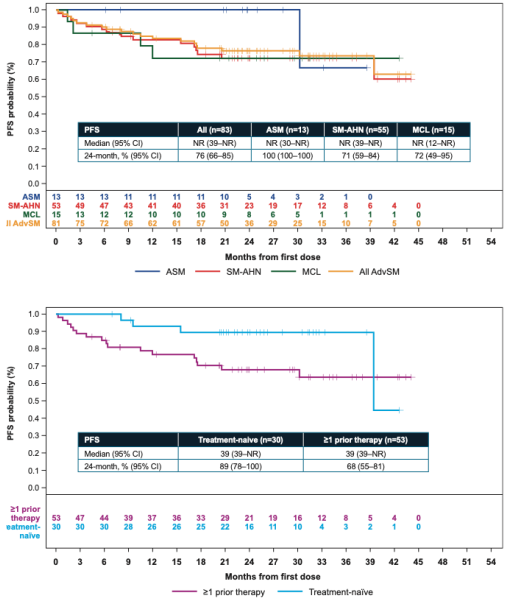
AVAPRITINIB

RESPONSE

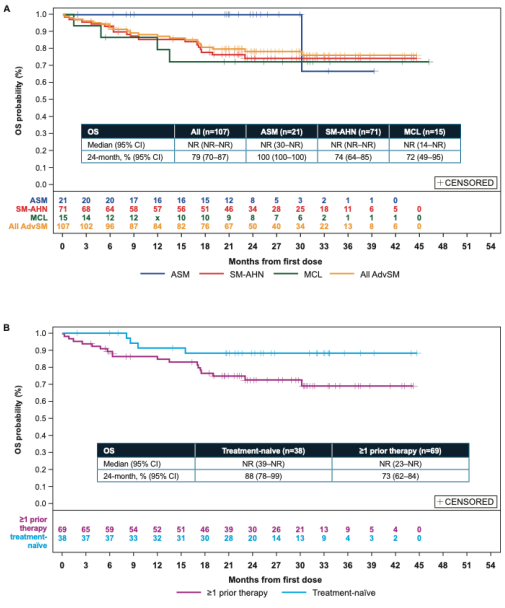
- Complete elimination of BM MC aggregates (70%)
- Reduction of serum tryptase <20 ng/mL (61%)
- *KIT* D816V <1% (58%)
- Palpable → non-palpable spleen (74%)
- **Mutations negative and BM, tryptase and/or *KIT* D816F VAF early!!! positive predictors of outcome**

PROGRESSION

- Frequently AHN, e.g. secondary AML
- Known and new somatic mutations



Progression-free survival according to subtype and prior treatment



Overall survival according to subtype and prior treatment

Gotlib et al., EHA 2023

Conclusion

- Several clinical end points, e.g. SVR35 and RBC-TI, have been shown to correlate with OS.
- Improvment of fibrosis and clonal disease burden as surrogates for PFS/OS have yet to be convincingly demonstrated.
- The JAK/STAT pathway remains a pivotal target but best end points and appropriate timing in the early stages of clinical trials may be different for JAKi combinations and novel pathways.
- Standardization and harmonization of inclusion criteria and response assessment is crucial in 1L but particularly 2L setting.
- Greatest impact will be observed when initiated early, before clonal evolution.

Modified from Vachhani et al., JCO 2021 & Pemmaraju et al., Cancer 2023