New Frontiers in the Targeted Treatment of Myelofibrosis

This activity is provided by Integrity Continuing Education, Inc.
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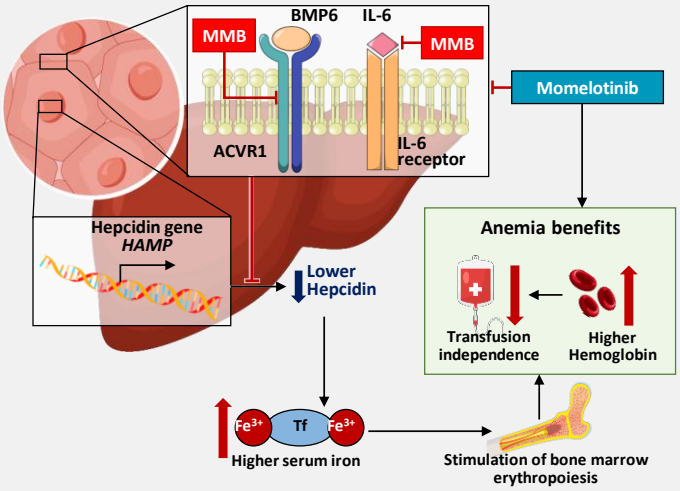
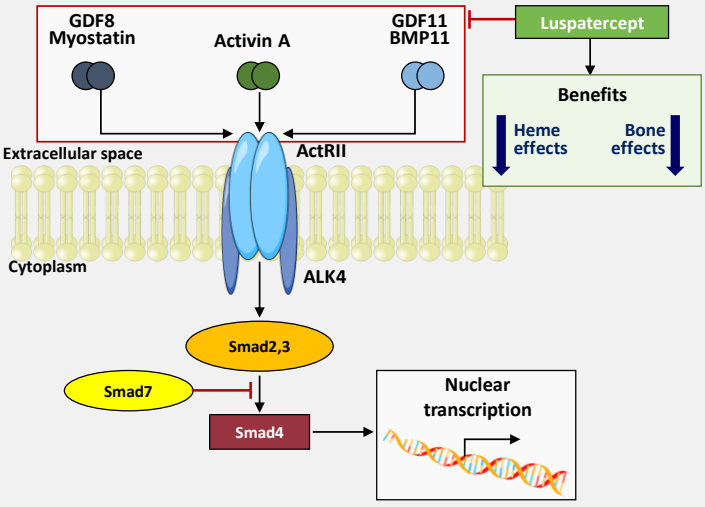
Brief Review of Novel Pathways and Mechanism of Action for New and Emerging Agents

Targets of Novel Therapeutics in the Management of Myelofibrosis – Momelotinib Inhibition of Hepcidin



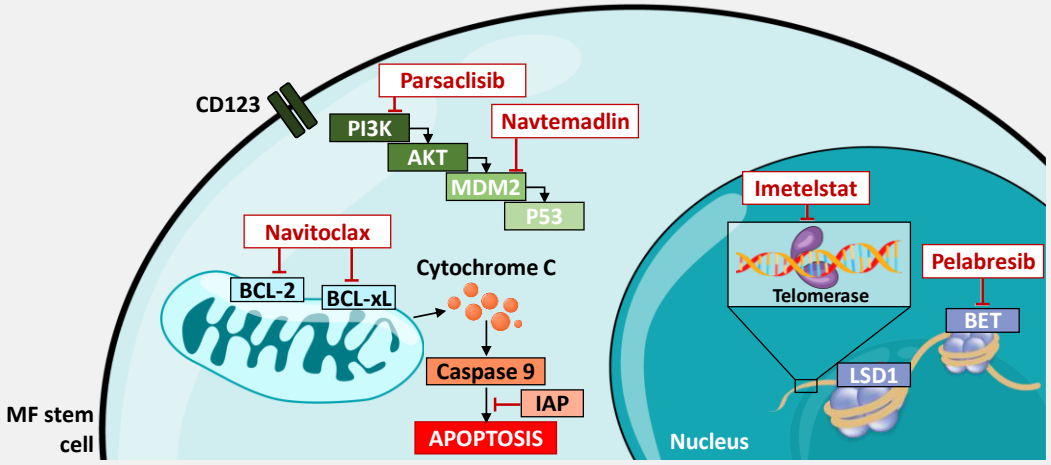
Chifotides HT, et al. *J Hematol Oncol.* 2022;15(1):7.

Targets of Novel Therapeutics in the Management of Myelofibrosis – Luspatercept Inhibition of TGFβ



Harrison CN, et al. *Future Oncol.* 2022;18(27):2987-2997.

Targets of Novel Therapeutics in the Management of Myelofibrosis



Tremblay D, Mascarenhas J. *Cells*. 2021;10(5):1034.

INTEGRITY CONTINUING EDUCATION

Second-Generation JAK Inhibitors

INTEGRITY CONTINUING EDUCATION

Articles Discussed

- Mesa RA, et al. Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial. *Lancet Haematol*. 2017.
- Verstovsek S, et al. Retrospective analysis of pacritinib in patients with myelofibrosis and severe thrombocytopenia. *Haematologica*. 2022.
- Harrison CN, et al. Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2018.
- Mesa RA, et al. SIMPLIFY-1: A phase III randomized trial of momelotinib versus ruxolitinib in janus kinase inhibitor-naive patients with myelofibrosis. *J Clin Oncol*. 2017.
- Mesa R, et al. Overall survival in the SIMPLIFY-1 and SIMPLIFY-2 phase 3 trials of momelotinib in patients with myelofibrosis. *Leukemia*. 2022.
- Verstovsek S, et al. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): results from an international, double-blind, randomized, controlled, phase 3 study. *Lancet*. 2023.

PERSIST-1/2: Week 24 Outcomes With Pacritinib vs BAT

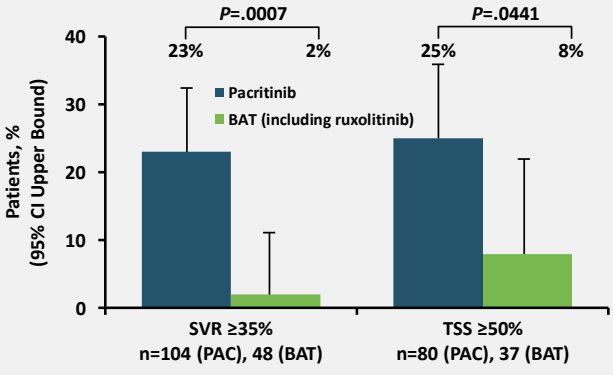
PERSIST-1 Sustained SVR and symptom reduction, regardless of baseline cytopenia

- SVR35: 19% vs 5% (*P*=.0003)
- TSS50: 19% vs 10% (*P*=.0027)

PERSIST-2 Twice daily PAC more effective than BAT in reducing splenomegaly and symptoms

- SVR35: 22% vs 3% (*P*=.001)
- TSS50: 32% vs 14% (*P*=.01)
- TI (retrospective):
  - 24% vs 5% (*P*=.013; SIMPLIFY criteria)
  - Identified as ACVR1 inhibitor

PERSIST-1/2: Retrospective Analysis of Response in Patients With Severe Thrombocytopenia



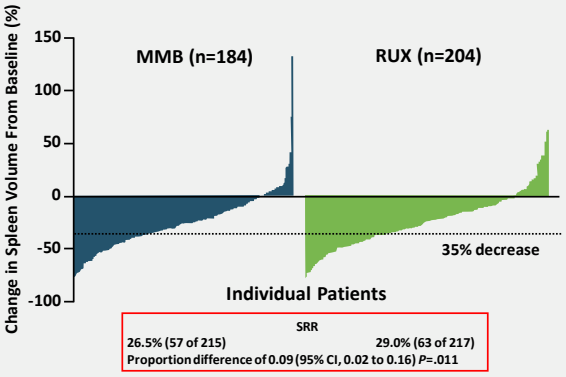
Pacritinib is a promising treatment for patients with severe thrombocytopenia

ACVT1, activin A receptor type 1; BAT, best available therapy; PAC, pacritinib; SVR, spleen volume reduction; TI, transfusion independence; TSS, total symptom score.

Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659; Mesa RA, et al. *Lancet Haematol*. 2017;4(5):e225-e236; Verstovsek S, et al. *Haematologica*. 2022;107(7):1599-1607.

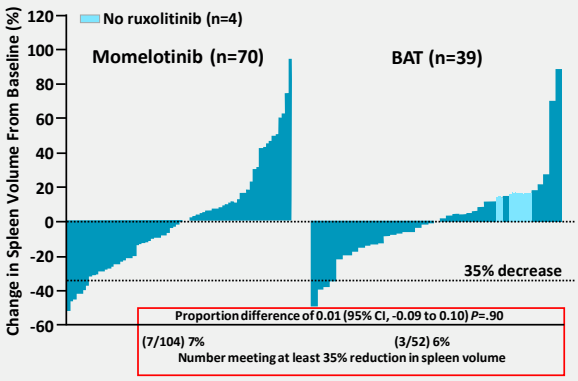
SIMPLIFY-1/2: Week 24 Outcomes With Momelotinib

SIMPLIFY-1 Spleen Volume and Response



MMB noninferior to RUX for spleen response but no symptom response (TSS50: 28% vs 42%)

SIMPLIFY-2 Spleen Volume and Response



MMB not superior to BAT for SVR35 but significantly improved TSS50 (26% vs 6%)

MMB, momelotinib; RUX, ruxolitinib; SRR, spleen response rate.

Harrison CN, et al. *Lancet Haematol*. 2018;5(2):e73-e81; Mesa RA, et al. *J Clin Oncol*. 2017;35(34):3844-3850.

SIMPLIFY-1/2: OS From Week 24 With MMB→MMB vs RUX→MMB

	SIMPLIFY-1	SIMPLIFY-2
TI vs non-TI (HR)		
MMB -> MMB	0.323*	0.771
RUX -> MMB	0.668	0.479
TSS-R vs TSS-NR (HR)		
MMB -> MMB	0.684	0.839
RUX -> MMB	0.637	0.982
SVR-R vs SVR-NR (HR)		
MMB -> MMB	0.796	NA
RUX -> MMB	0.450**	NA

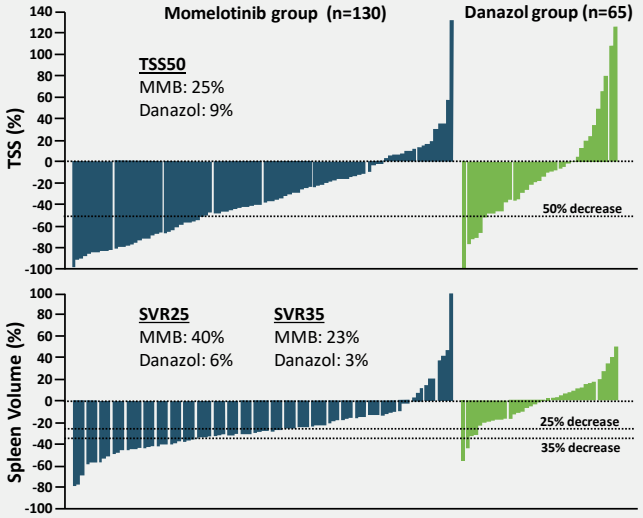
MMB is associated with excellent OS and LFS, regardless of initial randomization.

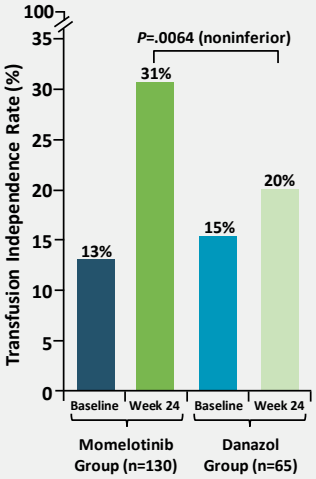
*P <.001; **P <.01

HR, hazard ratio; LFS, leukemia-free survival; OS, overall survival.

Mesa R, et al. *Leukemia*. 2022;36(9):2261-2268.

MOMENTUM: Week 24 Outcomes With Momelotinib vs Danazol





MMB demonstrated clinically significant improvements in MF-associated symptoms, anemia measures, and spleen response, especially in patients with anemia

Verstovsek S, et al. *Lancet*. 2023;401(10373):269-280.

INTEGRITY CONTINUING EDUCATION

Agents Targeting Cytopenias

INTEGRITY CONTINUING EDUCATION

Articles Discussed

- Gerds AT, et al. A phase 2 study of luspatercept in patients with myelofibrosis-associated anemia. *Blood*. 2019.
- Gerds AT, et al. Duration of response to luspatercept in patients (Pts) requiring red blood cell (RBC) transfusions with myelofibrosis (MF) - updated data from the phase 2 ACE-536-MF-001 study. *Blood*. 2020.

ACE-536-MF-001: Efficacy of Luspatercept in Transfusion-Dependent Patients

Efficacy of Luspatercept in TD Patients

	Cohort 2 (n=21) TD, no RUX	Cohort 3B (n=19) TD + RUX
RBC-TI ≥12 weeks, %	10	27
≥50% reduction in RBC transfusion burden over 12 weeks, within 24 weeks, %	38	46
Median time to first RBC-TI, days	1.5	37
mDOR, weeks	49	42
Clinical benefit, %	27	57

Clinically significant and durable activity with luspatercept ± RUX in patients with MF-associated anemia

mDOR, median duration of response; RBC-TI, red blood cell transfusion independence; TD, transfusion dependent.
Gerds AT, et al. *Blood*. 2019;134(Supplement_1):557; Gerds AT, et al. *Blood*. 2020;136(Supplement 1):47-48.

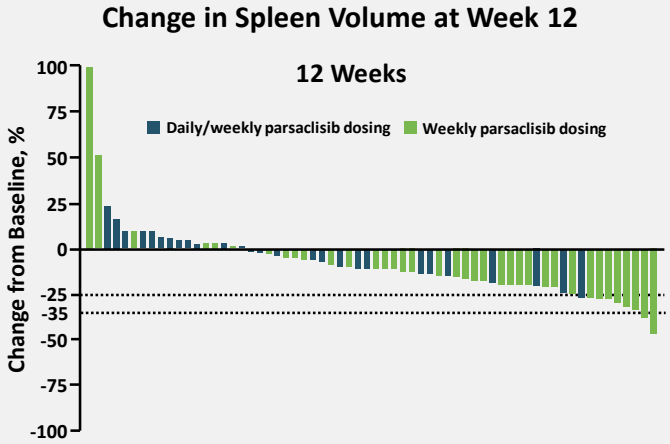
Agents Targeting Signal Transduction Pathways

Articles Discussed

- Yacoub A, et al. Efficacy and safety of add-on parsaclisib to ruxolitinib therapy in myelofibrosis patients with suboptimal response to ruxolitinib: Final results from a phase 2 study. *Blood*. 2022.
- Mascarenhas J, et al. MANIFEST: Pelabresib in combination with ruxolitinib for Jjanus kinase inhibitor treatment-naive myelofibrosis. *J Clin Oncol*. 2023.

INCB50465-201: Outcomes With Parsaclisib + RUX in Previously-Treated Patients

- Additional spleen volume reduction and improvement in symptom burden with add-on parsaclisib, greater efficacy and safety with daily dosing
- Week 12
  - SVR25: 3% vs 21%
  - SVR35: 0 vs 5%
  - TSS50: 19% vs 32%
- Week 24
  - SVR25: 13% vs 29%
  - SVR35: 3% vs 7%
  - TSS50: 19% vs 49%
- 22% continued open-label parsaclisib

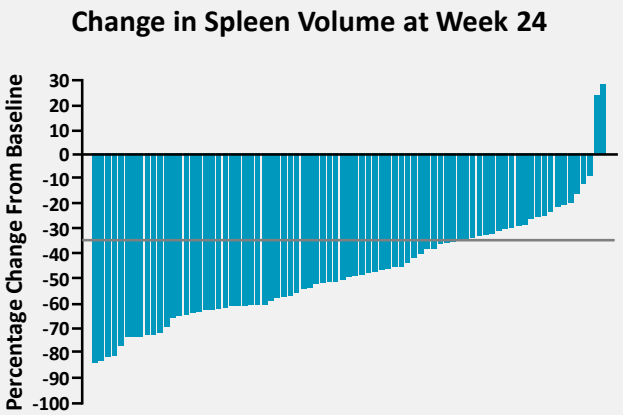


Yacoub A, et al. *Blood.* 2022;140(Supplement 1):579-582.

MANIFEST: Week 24 Outcomes With Pelabresib + RUX in JAKi-Naïve Patients

Durable improvements in spleen and symptom burden, with potential disease modifying activity

- SVR35: 68%
- TSS50: 56%
- ↑ Hb: 36%
- 95% continued combination therapy beyond week 24



Hb, hemoglobin; JAKi, Janus kinase inhibitor.
Mascarenhas J, et al. *J Clin Oncol.* 2023:JCO2201972.

Agents Targeting Apoptotic Pathways

Articles Discussed

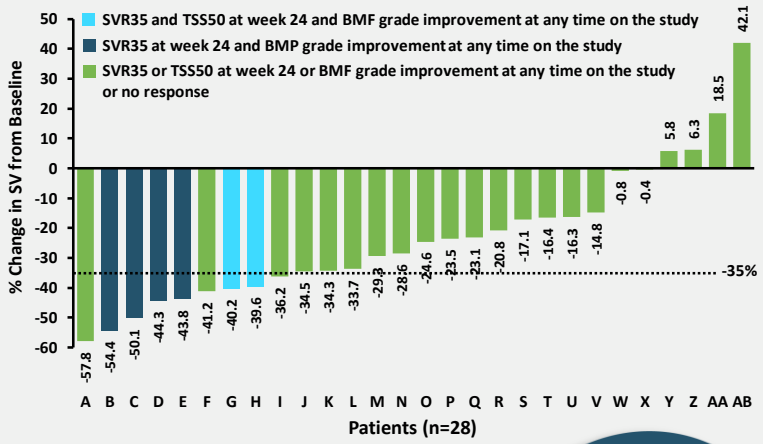
- Harrison CN, et al. Addition of navitoclax to ongoing ruxolitinib therapy for patients with myelofibrosis with progression or suboptimal response: Phase II safety and efficacy. *J Clin Oncol*. 2022.
- Vachani P, et al. Potential disease-modifying activity of navtemadlin (KRT-232), a first-in-class MDM2 inhibitor, correlates with clinical benefits in relapsed/refractory myelofibrosis (MF). *Blood*. 2021.
- Verstovsek S, et al. BOREAS: a global, phase III study of the MDM2 inhibitor navtemadlin (KRT-232) in relapsed/refractory myelofibrosis. *Future Oncol*. 2022.

REFINE: Week 24 Outcomes With Navitoclax + RUX in Previously-Treated Patients

Durable SVR35, and improved TSS50, Hb response, and BMF with the addition of navitoclax

- SVR35: 27%
- TSS50: 30%
- BMF grade ↓: 33%
- Anemia response: 64%
- mOS: NR (95% CI 26.1, NE)

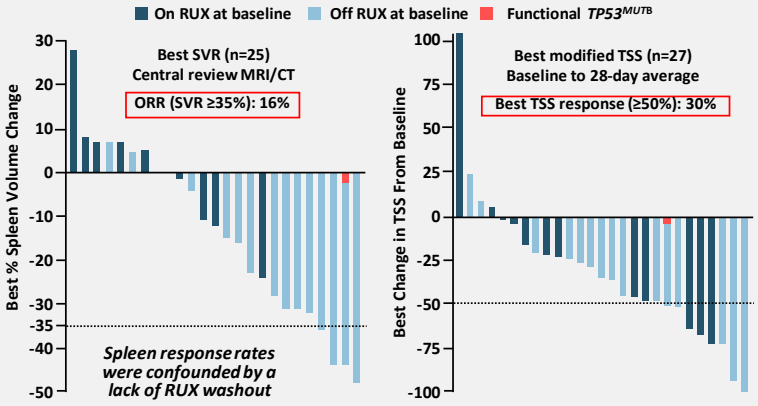
Change in Spleen Volume at Week 24



BMF, bone marrow fibrosis; mOS, median overall survival; NE, not estimable; NR, not reported; SV, spleen volume.
Harrison CN, et al. *J Clin Oncol*. 2022;40(15):1671-1680.

BOREAS: Outcomes With Navtemadlin in Previously-Treated Patients

Change in Spleen Volume and Response at Week 24



Spleen responses correlated with reductions of MPN-driver mutation burden, decreased peripheral CD34+ cell counts, improvements in BMF scores, and reduction in TNFα

- Best driver gene reduction ≥20%: 34%
- Complete VAF reduction* in HMR or driver genes: 29%
- SVR with ≥20% vs <20% decrease in driver VAFs: 32% vs 5% (*P*=.007)

Promising activity in patients with poor prognosis relapsed/refractory MF.
*Below limit of detection.
CT, computerized tomography; HMR, high-molecular risk; MPN, myeloproliferative neoplasm; MRI, magnetic resonance imaging; ORR, overall response rate; TNF, tumor necrosis factor; VAF, variant allele frequency.
Vachani P, et al. *Blood*. 2021;138(Supplement 1):3581; Verstovsek S, et al. *Future Oncol*. 2022;18(37):4059-4069.

Agents Targeting Telomerase

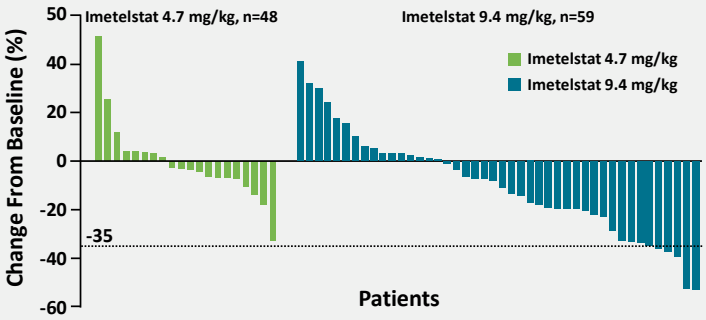
Article Discussed

- Mascarenhas J, et al. Randomized, single-blind, multicenter phase II study of two doses of imetelstat in relapsed or refractory myelofibrosis. *J Clin Oncol*. 2021.

IMbark: Week 24 Outcomes With Imetelstat in Patients With Relapsed or JAKi-Refractory Myelofibrosis

Clinical benefits in symptom response and potential disease modifying activity with two 9.4 mg/kg doses of imetelstat

Spleen Volume at Week 24



4.7 vs 9.4 mg/kg

- SVR35: 0 vs 10%
- TSS50: 6% vs 32%
- mOS: 19.9 vs 29.9 months

Response ± ≥20% VAF reduction

- Spleen: 13% vs 3%
- Symptom: 31% vs 24%
- BMF grade ↓: 54% vs 25%
- mOS: 31.6 vs 22.8 months

Mascarenhas J, et al. *J Clin Oncol*. 2021;39(26):2881-2892.